75590C 43 BC

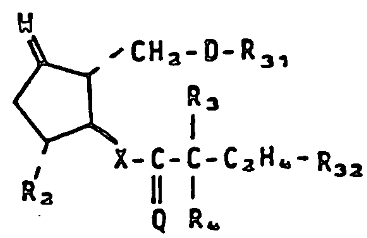
UK Patent Application (19) GB (11) 2 048 254 A

(21) Application No 8010083
(22) Date of filing 26 Mar 1980
(30) Priority data
(31) 25878
25899
26379
26083
(32) 2 Apr 1979
(33) United States of America (US)
(43) Application published 10 Dec 1980
(51) INT CL[3] C07C 177/00 A61K 31/557 C07C 33/12 49/172 C07D 307/935 309/12 C07F 9/40
(52) Domestic classification C2C 1175 147X 200 201 213 220 225 227 22Y 247 253 25Y 274 275 282 292 29Y 302 304 30Y 311 31Y 342 348 34Y 351 352 353 355 360 361 362 363 366 367 368 36Y 385 387 388 389 409 40Y 43X 490 491 500 503 509 50Y 512 514 52Y 573 623 625 628 62X 633 635 643 652 655 658 65X 662 665 668 66X 672 67X 695 761 767 774 778 779 802 80Y AA BW KQ SC TU UF UN WD WP WZ C2P 3B11B 3B14A 3B19E 7 9
(56) Documents cited
GB 1501864
GB 1388443
US 4127612A
US 4036876A
US 3956403A
US 3878046A
Fobs Letters 57 22 (1975)
Jacs 91 3685 (1969)
(58) Field of search C2C

(71) Applicants
The Upjohn Company, 301 Henrietta Street, Kalamazoo, Michigan 49001, United States of America
(72) Inventor
John Charles Sim
(74) Agents
Gill Jennings & Every

(54) **19,20-didehydro, 19-hydroxy and 19-oxo-prostaglandin derivatives**

(57) Prostaglandins of formula



wherein
R_{32} is $-CH{=}CH_2$, $-C.Me(OH)-CH_3$, $-CH(OH)-CH_3$ or $-CO-CH_3$.

Certain of the chemical formulae appearing in the printed specification were submitted in formal form after the date of filing.

GB 2 048 254 A

DT 3012 249

SPECIFICATION
Pr staglandin derivatives

This invention r lat s to prostaglandin d rivatives and to proc sses for preparing them.

For background on prostaglandins, see for xample Bergstrom et al., Pharmacol. R v. 20, 1 (1968). For nomenclature of the prostaglandins, se N. A. Nelson, J. M dic. Chem. 17, 911 (1974). With respect to the stereochemistry of substituent groups at C—15 herein, see R. S. Cahn, J. Chem. Ed. 41, 116 (1964).

As drawn herein the formulas represent a particular optically active isomer having the same absolute configuration as PGE_1 obtained from mammalian tissues.

In the formulas, broken line attachments to the cyclopentane ring or side chain indicate substituents in alpha configuration, i.e. below the plane of the ring or side chain. Heavy solid line attachments indicate substituents in beta configuration, i.e. above the plane.

Included in the background of chemical literature and patents are the following: K. Green et al., J. Lipid Res. 5, 117 (1969), PGE_3 and $PGF_3\alpha$, methyl esters; B. Samuelsson, U.S. Patent No. 3,657,316, 19-hydroxy-PGE_1; P. L. Taylor et al., Nature 250, 665 (1974) and FEBS Letters 57, 22 (1975), 19-hydroxy-PGE's and -PGF's; W. Marscheck et al., U.S. Patent No. 3,878,046, 11-deoxy-19-hydroxy-PGE_2; C. J. Sih et al., J. Am. Chem. Soc. 91, 3685 (1969), 19-oxo-PGE_2 and -13,14-dihydro-PGE_1; J. C. Sih, Prostaglandins 13, 831 (1977), (19R)-19-hydroxy-PGE_1, -PGE_2, -$PGF_1\alpha$, and -$PGF_2\alpha$; Brit. Patent Spec. No. 1,388,443, Derwent Farmdoc Abstract No. 00520U, reduction of 9,19-diketoprostanoic acids; A. F. Marx et al., U.S. Patent No. 4,054,595, 18- and 19-hydroxy-prostaglandins; J. E. Pike, U.S. Patent No. 3,922,297, 19-methyl-prostaglandins; R. K. Beerthuis et al., Rec. Trav. Chim. Pays. Bas 90, 943 (1971), cis-Δ^{18}-PGE_1; K. G. Untch et al., J. Am. Chem. Soc. 100, 6211 (1978), dl-19-hydroxy-PGE_1 and dl-13-cis-15-epi-19-hydroxy-PGE_1; German Offenleg. 2,505,519 (Derwent Farmdoc Abstract No. 56027W) or Chem. Abs. 84, 43441w, 20-hydroxy-PGE_2 or -$PGF_2\alpha$.

Subsequent to this invention there appeared U.S. Patent No. 4,127,612 to H. C. Kluender et al. for 2-decarboxy-2-hydroxymethyl-19-hydroxy-PGE_1 and 19-hydroxy PGE_1 carbinol analogues.

It is the purpose of this invention to provide novel products having pharmacological activity. It is a further purpose to provide a process for preparing these products and their intermediates. More specifically, there are provided certain prostaglandin derivatives having a 19,20-didehydro, a 19-hydroxy, or a 19-keto feature.

Accordingly there are provided compounds of formula III, wherein the terms D, Q, R_{31}, and the like are defined in the TABLE OF DEFINITION OF TERMS FOR FORMULAS herein, together with other terms used hereinafter.

The products of this invention within the scope of formula III are extremely potent in causing various biological responses. For that reason, these compounds are useful for pharmacological purposes. A few of those biological responses are: inhibition of blood platelet aggregation, inhibition of gastric secretion and reduction of undesirable gastrointestinal effects from systemic administration of prostaglandin synthetase inhibitors, controlling spasm and facilitating breathing in asthmatic conditions, and decongesting nasal passages.

Because of these biological responses, these novel compounds are useful to study, prevent, control, or alleviate a wide variety of diseases and undesirable physiological conditions in mammals, including humans useful domestic animals, pets, and zoological specimens, and in laboratory animals, for example, mice, rats, rabbits and monkeys.

These compounds are useful whenever it is desired to inhibit platelet aggregation, to reduce the adhesive character of platelets, and to remove or prevent the formation of thrombi in mammals, including man, rabbits, and rats. For example, these compounds are useful in the treatment and prevention of myocardial infarcts, to treat and prevent post-operative surgery, and to treat conditions such as arthrosclerosis, arteriosclerosis, blood clotting defects due to lipemia, and other clinical conditions in which the underlying etiology is associated with lipid imbalance or hyperlipidemia. Other *in vivo* applications include geriatric patients to prevent cerebral ischemic attacks and long term prophylaxis following myocardial infarcts and strokes. For these purposes, these compounds are administered systemically, e.g., intravenously, subcutaneously, intramuscularly, and in the form of sterile implants for prolonged action. For rapid response, especially in emergency situations, the intravenous route of administration is preferred. Doses in the range of about 0.01 to about 10 mg. per kg. of body weight per day are used, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

The addition of th se compounds to whole blood provides *in vitro* applications such as storage f whole blood to be used in h art-lung machines. Addit nally wh l blood containing these compounds can be circulated through limbs and organs, .g. heart and kidneys, whether attached to the original body, detached and being preserved r prepared for transplant, r attached t a new body. Blocking of aggregated platelets is avoided by the presence f these compounds. For this purpose, the compound is add d gradually r in singl or multiple portions t the circulating blood, to the blood of the donor p rson or animal, to the perfused body portion, attached or detached, to the recipient, or to two or all of those at a total steady state dose of about 0.001 — 1.0 μg./ml. of whole

blood. These compounds are aiso useful in preparing plat l t-rich concentrates from blood for us in treating thrombocytopenia or in chemoth rapy.

These compounds are also useful in mammals, including man and certain us ful animals, e.g. dogs and pigs, to reduce and control xc ssiv gastric secretion, thereby to reduce or avoid gastrointestinal ulcer formation, and accelerate the h aling of such ulcers already pres nt in the gastroint stinal tract. For this purpos , these compounds are inj cted or infused intravenously, subcutaneously, or intramuscularly in an infusion dos range of about 0.01 to about 10 mg. p r kg. of body weight p r day, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

These compounds are also useful in reducing the undesirable gastrointestinal effects resulting from systemic administration of anti-inflammatory prostaglandin synthetase inhibitors, and are used for that purpose by concomitant administration of the formula III—VI compound and the anti-inflammatory prostaglandin synthetase inhibitor. See Partridge et al., U.S. Pat. No. 3,781,429, for a disclosure as to the administration of certain prostaglandins of the E and A series. The anti-inflammatory synthetase inhibitor, for example indomethacin, aspirin, or phenylbutazone is administered in any of the ways known in the art to alleviate an inflammatory condition, for example, in any dosage regimen and by any of the known routes of systemic administration. The formula III compound is administered along with the anti-inflammatory prostaglandin synthetase inhibitor either by the same route of administration or by a different route. The dosage regimen for the formula III compound in accord with this treatment will depend upon a variety of factors, including the type, age, weight, sex and medical condition of the mammal, the nature and dosage regimen of the anti-inflammatory synthetase inhibitor being administered to the mammal, and the sensitivity of the particular formula III compound to be administered. For example, not every human in need of an anti-inflammatory substance experiences the same adverse gastrointestinal effects when taking the substance. The gastrointestinal effects will frequently vary substantially in kind and degree. But it is within the skill of the attending physician or veterinarian to determine that administration of the anti-inflammatory substance is causing undesirable gastrointestinal effects in the human or animal subject and to prescribe an effective amount of the formula III compound to reduce and then substantially to eliminate those undesirable effects.

These compounds are also useful in the treatment of asthma. For example they are useful as bronchodilators or as inhibitors of mediators, such as SRS—A, and histamine which are released from cells activated by an antigen-antibody complex. Thus, these compounds control spasm and facilitates breathing in conditions such as bronchial asthma, bronchitis, bronchiectasis, pneumonia and emphysema. For these purposes, these compounds are administered in a variety of dosage forms, e.g., orally in the form of tablets, capsules, or liquids; rectally in the form of suppositories; parenterally, subcutaneously, or intramuscularly, with intravenous administration being preferred in emergency situations; by inhalation in the form of aerosols or solutions for nebulizers; or by insufflation in the form of powder. Doses in the range of about 0 01 to 5 mg. per kg. of body weight are used 1 to to 4 times a day, the exact dose depending on the age, weight and condition of the patient and on the frequency and route of administration. For the above use the compound can be combined advantageously with other anti-asthmatic agents, such as sympathomimetics (isoproterenol, phenylephrine, ephedrine, etc.), xanthine derivatives (theophylline and aminophylline), and corticosteroids (ACTH and prednisolone).

These compounds are effectively administered to human asthma patients by oral inhalation or by aerosol inhalation. For administration by the oral inhalation route with conventional nebulizers or by oxygen aerosolization it is convenient to provide the formula III ingredient in dilute solution, preferably at concentrations of about 1 part of medicament to from about 100 to 200 parts by weight of total solution. Entirely conventional additives may be employed to stabilize these solutions or to provide isotonic media, for example, sodium chloride, sodium citrate, citric acid, and the like can be employed. For administration as a self-propelled dosage unit for administering the active ingredient in aerosol form suitable for inhalation therapy the composition can comprise the active ingredient suspended in an inert propellant (such as a mixture of dichlorodifluoromethane and dichlorotetrafluoroethane) together with a co-solvent, such as ethanol, flavoring materials and stabilizers. Instead of a co-solvent there can also be used a dispensing agent such as oleyl alcohol. Suitable means to employ the aerosol inhalation therapy technique are described fully in U.S. 2,868,691 for example.

These compounds are useful in mammals, including man, as nasal decongestants and are used for this purpose in a dose range of about 10 μg to about 10 mg. per ml. of a pharmacologically suitable liquid vehicle or as an aerosol spray, both for typical application.

These compounds are also useful in treating peripheral vascular disease in humans. The term peripheral vascular disease as used herein means disease of any of the blood vessels outside of the heart and to disease of th lymph v ss ls, for example, frostbite, ischemic cerebrovascular disease, arteriovenous, fistulas, isch mic leg ulcers, phl bitis, venous insufficiency, gangrene, hepatorenal syndrome, ductus arteriosus, non-obstructive m senteric ischemia, arteritis lymphangitis and th like. The xamples are included t be illustrat d and sh uld not be construed as limiting th t rm peripheral vascular disease. For these conditi ns the compounds are administer d orally or parent rally via inj ction or infusion directly into a vein r artery. The dosages of such compounds are in the rang of 0.01—1.0 μg. administ red by infusions at an hourly rate or by

SPECIFICATION

Prostaglandin derivatives

This invention relates to prostaglandin derivatives and to processes for preparing them.

For background on prostaglandins, see for example Bergstrom et al., Pharmacol. Rev. 20, 1 (1968). For nomenclature of the prostaglandins, see N. A. Nelson, J. Medic. Chem. 17, 911 (1974). With respect to the stereochemistry of substituent groups at C—15 herein, see R. S. Cahn, J. Chem. Ed. 41, 116 (1964).

As drawn herein the formulas represent a particular optically active isomer having the same absolute configuration as PGE_1 obtained from mammalian tissues.

In the formulas, broken line attachments to the cyclopentane ring or side chain indicate substituents in alpha configuration, i.e. below the plane of the ring or side chain. Heavy solid line attachments indicate substituents in beta configuration, i.e. above the plane.

Included in the background of chemical literature and patents are the following: K. Green et al., J. Lipid Res. 5, 117 (1969), PGE_3 and $PGF_3\alpha$, methyl esters; B. Samuelsson, U.S. Patent No. 3,657,316, 19-hydroxy-PGE_1; P. L. Taylor et al., Nature 250, 665 (1974) and FEBS Letters 57, 22 (1975), 19-hydroxy-PGE's and -PGF's; W. Marscheck et al., U.S. Patent No. 3,878,046, 11-deoxy-19-hydroxy-PGE_2; C. J. Sih et al., J. Am. Chem. Soc. 91, 3685 (1969), 19-oxo-PGE_2 and -13,14-dihydro-PGE_1; J. C. Sih, Prostaglandins 13, 831 (1977), (19R)-19-hydroxy-PGE_1, -PGE_2, -$PGF_1\alpha$, and -$PGF_2\alpha$; Brit. Patent Spec. No. 1,388,443, Derwent Farmdoc Abstract No. 00520U, reduction of 9,19-diketoprostanoic acids; A. F. Marx et al., U.S. Patent No. 4,054,595, 18- and 19-hydroxy-prostaglandins; J. E. Pike, U.S. Patent No. 3,922,297, 19-methyl-prostaglandins; R. K. Beerthuis et al., Rec. Trav. Chim. Pays. Bas 90, 943 (1971), cis-Δ^{19}-PGE_1; K. G. Untch et al., J. Am. Chem. Soc. 100, 6211 (1978), dl-19-hydroxy-PGE_1 and dl-13-cis-15-epi-19-hydroxy-PGE_1; German Offenleg. 2,505,519 (Derwent Farmdoc Abstract No. 58027W) or Chem. Abs. 84, 43441w, 20-hydroxy-PGE_2 or -$PGF_2\alpha$.

Subsequent to this invention there appeared U.S. Patent No. 4,127,612 to H. C. Kluender et al. for 2-decarboxy-2-hydroxymethyl-19-hydroxy-PGE_1 and 19-hydroxy PGE_1 carbinol analogues.

It is the purpose of this invention to provide novel products having pharmacological activity. It is a further purpose to provide a process for preparing these products and their intermediates. More specifically, there are provided certain prostaglandin derivatives having a 19,20-didehydro, a 19-hydroxy, or a 19-keto feature.

Accordingly there are provided compounds of formula III, wherein the terms D, Q, R_{31}, and the like are defined in the TABLE OF DEFINITION OF TERMS FOR FORMULAS herein, together with other terms used hereinafter.

The products of this invention within the scope of formula III are extremely potent in causing various biological responses. For that reason these compounds are useful for pharmacological purposes. A few of those biological responses are: inhibition of blood platelet aggregation, inhibition of gastric secretion and reduction of undesirable gastrointestinal effects from systemic administration of prostaglandin synthetase inhibitors, controlling spasm and facilitating breathing in asthmatic conditions, and decongesting nasal passages.

Because of these biological responses, these novel compounds are useful to study, prevent, control, or alleviate a wide variety of diseases and undesirable physiological conditions in mammals, including humans, useful domestic animals, pets, and zoological specimens, and in laboratory animals, for example, mice, rats, rabbits and monkeys.

These compounds are useful whenever it is desired to inhibit platelet aggregation, to reduce the adhesive character of platelets, and to remove or prevent the formation of thrombi in mammals, including man, rabbits, and rats. For example, these compounds are useful in the treatment and prevention of myocardial infarcts, to treat and prevent post-operative surgery, and to treat conditions such as arthrosclerosis, arteriosclerosis, blood clotting defects due to lipemia, and other clinical conditions in which the underlying etiology is associated with lipid imbalance or hyperlipidemia. Other *in vivo* applications include geriatric patients to prevent cerebral ischemic attacks and long term prophylaxis following myocardial infarcts and strokes. For these purposes, these compounds are administered systemically, e.g., intravenously, subcutaneously, intramuscularly, and in the form of sterile implants for prolonged action. For rapid response, especially in emergency situations, the intravenous route of administration is preferred. Doses in the range of about 0.01 to about 10 mg. per kg. of body weight per day are used, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

The addition of these compounds to whole blood provides *in vitro* applications such as storage of whole blood to be used in heart-lung machines. Additonally whole blood containing these compounds can be circulated through limbs and organs, e.g. heart and kidneys, whether attached to the original body, detached and being preserved or prepared for transplant, or attached to a new body. Blocking of aggregated platelets is avoided by the presence of these compounds. For this purpose, the compound is added gradually or in single or multiple portions to the circulating blood, to the blood of the donor person or animal, to the perfused body portion, attached or detached, to the recipient, or to two or all of those at a total steady state dose of about 0.001 — 1.0 μg./ml. of whole

injection on a daily basis, i.e. 1—4 times a day, the exact dose depending on the age, weight, and condition of the patient and on the frequency and route of administration. Treatment is continued for one to five days, although three days is ordinarily sufficient to assure long-lasting therapeutic action. In the event that systemic or side effects are observed the dosage is lowered below the threshold at which such systemic or side effects are observed. These compounds are accordingly useful for treating peripheral vascular diseases in the extremities of humans who have circulatory insufficiencies in said extremities, such treatment affording relief of rest pain and induction of heating of ulcers. For a complete discussion of the nature of and clinical manifestations of human peripheral vascular disease and the method previously known of its treatment with prostaglandins see South African Patent No. 74/0149 referenced as Derwent Farmdoc No. 58400V. See Elliot et al., Lancet, January 18 1975, pp. 140—142.

Surprisingly, the formula IV compounds have little or no efect on stimulation of smooth muscle. The formula-III 19,20-didehydro compounds, however, are extremely potent in causing stimulation of smooth muscle.

The formula-III 19.20-didehydro compounds are not only active in causing stimulation of smooth muscle, but are also highly active in potentiating other known smooth muscle stimulators, for example, oxytocic agents, e.g., oxytocin, and the various ergot alkaloids including derivatives and analogs thereof. Therefore, they are useful in place of or in combination with less than usual amounts of these known smooth muscle stimulators, for example, to relieve the symptoms of paralytic ileus, or to control or prevent atonic uterine bleeding after abortion or delivery, to aid in expulsion of the placenta, and during the puerperium. For the latter purpose, the compound is administered by intravenous infusion immediately after abortion or delivery at a dose in the range about 0.01 to about 50 μg. per kg. of body weight per minute until the desired effect is obtained. Subsequent doses are given by intravenous, subcutaneous, or intramuscular injection or infusion during puerperium in the range of 0.01 to 2 mg. per kg. of body weight per day, the exact dose depending on the age, weight, and condition of the patient or animal.

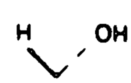
The formula-III 19,20-didehydro compounds are useful in place of oxytocin to induce labor in pregnant female animals, including man, cows, sheep, and pigs, at or near term, or in pregnant animals with intrauterine death of the fetus from about 20 weeks to term. For this purpose, the compound is infused intravenously at a dose of 0.01 to 50μ per kg. of body weight per minute until or near the termination of the second stage of labor, i.e., expulsion of the fetus. These compounds are especially useful when the female is one or more weeks post-mature and natural labor has not started, or 12 to 60 hours after the membranes have ruptured and natural labor has not yet started. An alternative route of administration is oral.

The formula-III 19,20-didehydro compounds are further useful for controlling the reproductive cycle in menstruating female mammals including humans. By the term menstruating female mammals is meant animals which are mature enough to menstruate, but not so old that regular menstruation has ceased. For that purpose the compound is administered systematically at a dose level in the range of 0.01 mg. to about 20 mg. per kg. of body weight of the female mammal, advantageously during a span of time starting approximately at the time of ovulation and ending approximately at the time of mensus or just prior to mensus. Intravaginal and intrauterine routes are alternate methods of administration. Additionally, expulsion of an embryo or a fetus is accomplished by similar administration of the compound during the first or second trimester of the normal mammalian gestation period.

The formula-III 19,20-didehydro compounds are further useful in causing cervical dilation in pregnant and non-pregnant female mammals for purposes of gynecology and obstetrics. In labor induction and in clinical abortion produced by these compounds, cervical dilation is also observed. In cases of infertility, cervial dilation produced by these compounds is useful in assisting sperm movement to the uterus. Cervical dilation by these compounds is also useful in operative gynecology such as D and C (Cervical Dilation and Uterine Curettage) where mechanical dilation may cause perforation of the uterus, cervical tears, or infections. It is also useful for diagnostic procedures where dilation is necessary for tissue examination. For these purposes, the compound is administered locally or systemically. The compound, for example, is administered orally or vaginally at doses of about 5 to 50 mg. per treatment of an adult female human, with from one to five treatments per 24 hour period. Alternatively the compound is administered intramuscularly or subcutaneously at doses of about one to 25 mg. per treatment. The exact dosages for these purposes depend on the age, weight, and condition of the patient or animal.

There are further provided the various processes for preparing the compounds of formula III. Thus, for the 19.20-didehydro compounds of formula III, a process illustrated by Chart I comprises the steps of starting with a lactone of formula VIII and (a) transforming that starting compound to a compound of formula IX, (b) optionally oxidizing the product of step (a) to form a compound of formula XI and (c) transforming the compound IX or compound XI to a compound of formula III.

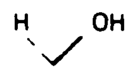
For PGFα-type formula-III compounds wherein W is



and R_1 is $-COOR_6$, also represented by formula X in Chart 1, the blocking groups of IX are simply removed by hydrolysis and the carboxyl group is optionally esterified. For PGE-type formula-III compounds wherein W is

$$\overset{O}{\|}$$

and R_1 is $-COOR_6$, represented by formula XII in Chart 1, the same procedures are applied to XI. For PGF_β-type compounds wherein W is



and R_1 is $-COOR_6$, the formula-XI compounds are reduced to a mixture of PGF_α and PGF_β compounds, whereupon the PGF_β-type compounds are separated, hydrolyzed to remove blocking groups, and optionally esterified. For 9-deoxo-9-methylene-PGE compounds of formula III wherein W is

$$\overset{CH_2}{\|}$$

also represented by formula XIV in Chart 1, the 9-oxo group of formula-XI is transformed to a 9-methylene moiety applying the sulfoximine procedure of C. A. Johnson et al., J. Am. Chem. Soc. 95, 6462 (1973), to yield XIII and XIV.

Transformation at C-1 and C-2 to alcohol, amine, amide, or tetrazolyl groups within the scope of R_1 are made by methods known in the art or disclosed herein. Likewise, transformations at D, Q, and X are made by methods known in the art or disclosed herein.

For the 19-hydroxy compounds of formula III, several processes are available. One process comprises the steps of starting with a lactone of formula XV and (a) transforming that starting material to a compound of formula XVI, (b) optionally oxidizing the product of step (a) to form a compound of formula XVII and (c) transforming compounds XVI or XVII to a compound of formula IV. When the lactone starting materials of formula XV are replaced with mixed C-19(R,S) epimers of formula XVa the corresponding mixed C-19 epimeric products of formula IVa are obtained.

Another process for the mixed C-19 epimeric products of formula IVa comprises the steps of starting with a 19,20-didehydro compound of formula XVIII (a) hydroxylating it to form a compound of formula a compound of formula XIX and (b) transforming the product of step (a) to a compound of formula XX.

For the 19-keto compounds of formula III, a process comprises the steps of starting with a 19-hydroxy compound of formula XXI or a mixed C-19 epimeric hydroxy compound of formula XIX and (a) oxidizing either compound XXI or XIX to form a 19-keto compound of formula XXII and (b) transforming the product of step (a) to a compound of formula V.

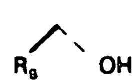
For the 19-hydroxy-19-methyl compounds of formula III, one process comprises the steps of starting with a lactone of formula XV or of formula XVa and (a) transforming that lactone to a compound of formula XXIII, (b) transforming the product of step (a) to a compound of formula XXIV and (c) transforming the product of step (b) to a 19-hydroxy-19-methyl compound of formula III.

Still another process for the 19-hydroxy-19-methyl compounds comprises the steps of starting with a 19-keto compound of formula XXII and (a) transforming it to a compound of formula XXV and (b) transforming the product of step (a) to a 19-hydroxy-19-methyl compound of formula III.

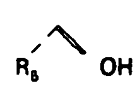
As with the formula-III 19-hydroxy-19-methyl compounds, the transformations of one compound to another with variations of D, Q, W, X, and, at C-1, of R_1 or R_{10}, are made for the formula-IV, -V, or -VI compounds by methods known in the art or disclosed herein, using appropriate blocking groups.

Charts 1-49, herein, illustrate the above processes and transformations. Those processes not illustrated are based on chemical procedures generally known to those skilled in the art. The steps of the charts will be discussed in detail below and further illustrated in the Examples.

To obtain the optimum combination of biological response specificity, potency, and duration of activity, certain compounds within the scope of formula III are preferred. For example it is preferred that Q be



wherein it is especially preferred that R_8 be hydrogen or methyl. When Q is



it is preferred that R_8 be methyl.

Another preference for the compounds of formula III, as to R_1, is that R_0 in —$COOR_0$ be either hydrogen or alkyl of one to 12 carbon atoms, inclusive, or a salt f a pharmacologically acceptable cation. Further, when R_0 is alkyl, it is m re preferred that it be alkyl of one t 4 carbon atoms, and specially methyl or ethyl.

Still anoth r preference for th 19-hydroxy and 19-hydroxy-19-methyl compounds f formula III is that the 19-hydroxy configuration be "R".

19,20-Didehydro Prostaglandin Compounds

This section will take up the procedures for preparing the formula-III 19,20 didehydro ("Δ^{19}") prostaglandin compounds and intermediates illustrated by charts 1—21.

Referring to Chart 1, starting materials of formula VIII are lactones readily prepared from known materials by processes shown in Charts 2—5, and these processes will be discussed at this point. In Chart 2 the formula-XXVI aldehyde is reacted with a Grignard reagent of the formula $CH_2{=}CH{—}(CH_2)_3{—}$ Mg-Hal and the resulting compound XXVII is blocked to form XXVIII. The starting aldehyde XXVI is known in the art (for example see Derwent Farmdoc Abstract No. 28225W, Japanese Patent No. 50—18460) or is available by the process in Chart 6, herein, and Preparation 1 (see also Derwent Farmdoc Abstract No. 56066Y, German Patent No. 2703471).

In Chart 6, tricyclic lactone aldehyde XXIX is available from U.S. Patent No. 3,816,462; either the exo or endo form will yield the formula-XXXII compound. In step (a) compound XXX is formed by the Wittig reaction with the ylid derived from methyltriphenylphosphonium bromide. In step (b) compound XXXI is obtained by hydroxylation. The formula-XXXII diester is then made by stepwise reaction, first using an ortho ester to form a cyclic ortho ester which is then reacted with anhydrous formic acid. Compound XXXIII is obtained in step (d) by solvolysis to remove formyl groups and, for XXXIV, free hydroxyl gorups are blocked in step (e). Acyl groups of XXXIV are removed by basic solvolysis in step (f) and, finally the terminal hydroxyl groups of XXXV are oxidized to form XXXVI in step (g).

In Chart 2, and hereafter, blocking group R_{10}, is as defined in the Table, but preferably is tetrahydropyranyl (THP). Formula-XXVI compounds wherein R_{10} is not THP are readily obtained from XXXVI of Chart 6 by replacing THP with hydrogen by mild acid hydrolysis and thereafter blocking with an appropriate form of R_{10} as follows.

When the blocking group R_{10} is tetrahydropyranyl (THP) or tetrahydrofuranyl, the appropriate reagent, e.g. 2,3-dihydropyran or 2,3-dihydrofuran, is used in an inert solvent such as dichloromethane in the presence of an acid condensing agent such as p-toluenesulfonic acid or pyridine hydrochloride. The reagent is used in slight excess, preferably 1.0 to 1.2 times theory, and the reaction is carried out at about 20—50°C.

When R_{10} is of the formula $R_{21}{—}O{—}\overset{|}{C}(R_{22}){—}CH_{23}R_{24}$, as defined herein, including 1-ethoxyethyl, the appropriate reagent is a vinyl ether, e.g. ethyl vinyl ether isopropenyl methyl ether, isobutyl vinyl ther, or any vinyl ether of the formula $R_{21}{—}O{—}C(R_{22}){=}CR_{23}R_{24}$ wherein R_{21}, R_{22}, R_{23}, and R_{24} are as defined herein; or an unsaturated cyclic or heterocyclic compound, e.g., 1-cyclohex-1-yl methyl ether or 5,6-dihydro-4-methoxy-2H-pyran. See C. B. Reese et al., J.Am. Chem. Soc. 89, 3366 (1967). The reaction conditions for such vinyl ethers and unsaturates are similar to those for dihydropyran above.

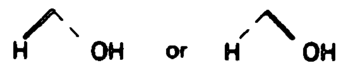
Again referring to Chart 2, if R_0 in Q_1 is alkyl, e.g. methyl, compound XXVII is oxidized with Jones reagent to form the 3′-oxo compound which is then reacted with a Grignard reagent or other appropriate organometallic reagent to introduce the alkyl group. See for example U.S. Patent No. 3,728,382. The 3′R and 3′S isomers are separated, for example by silica gel chromatography. Compound XXVIII is then obtained by blocking.

In Chart 3 an aldehyde of formula XXXVII is used. It is available, for example when R_{14} is acetyloxy, from E. J. Corey et al., J. Am. Chem. Soc. 91, 5675 (1969); when R_{14} is benzoyloxy, from U.S. Patent 3,778,450; when R_{14} is hydrogen, see E. J. Corey et al., Tetrahedron Lett. No. 49, 4753 (1971); when R_{14} is —CH_2OR_{10}, i.e. blocked hydroxymethyl, by blocking the hydroxymethyl-substituted lactone, for which see Derwent Farmdoc Abstract No. 12714W. In step (a), aldehyde XXXVII is reacted with a Witting reagent derived from a phosphonate of formula CLX

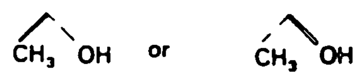
$$(CH_3O)_2\overset{\overset{\large O}{\|}}{P}{—}CH_2{—}\overset{\overset{\large O}{\|}}{C}{—}\underset{\underset{\large R_4}{|}}{\overset{\overset{\large R_3}{|}}{C}}{—}(CH_2)_2{—}CH{=}CH_2 \qquad \text{CLX}$$

to form compound XXXVIII. For further details of the Wittig reaction see, for example, A. William Johnson, "Ylid Chemistry", Academic Press, N.Y., 1966.

For intermediates of f rmula XXXIX in which Q is



th 3'-oxo group of XXXVIII is reduced in st p b, for example with zinc borohydride and the isomers are separated, for example by silica gel chromatography. The $3'_\alpha$ isomers are generally preferred. For intermediates in which Q is



the compound XXXVIII is reacted with a Grignard reagent CH_3MgHal or with trimethylaluminum and the isomers are separated by silica gel chromatography.

In step (c) the carboxyacyl blocking groups are removed by hydrolysis and hydroxyls are blocked with R_{15} blocking groups such as tetrahydropyranyl to form XL.

Compounds of formula XL are within the scope of formula VIII of Chart 1 and are accordingly useful as starting material therein. The remaining steps of Chart 3 produce compounds XLIV which correspond to formula VIII wherein X is $—CH_2CH_2—$.

In step (d) intermediate XLI is formed by hydroboration, for example with 9-borabicyclo[3.3.1]nonane ("9-BBN"), for which see Fieser et al., "Reagents for Organic Synthesis", Vol. 2, p. 31, 1969, Wiley and Sons, N.Y.

In step (e) compound XLI is reduced catalytically for example with hydrogen at atmospheric pressure over palladium on charcoal to yield XLII.

In step (f) the terminal hydroxy is mesylated or tosylated, for example, using methanesulfonyl chloride or p-toluenesulfonyl chloride in the presence of a tertiary base such as triethylamine or pyridine to yield XLIII, and finally in step (g) the olefin is restored by methods known in the art. For example, the sulfonate is reacted with the sodium derivative of phenyl selenide and the resulting phenyl selenide is oxidized with excess hydrogen peroxide. See Fieser et al., ibid, Vol. 5, p. 273, 1975. Compounds XLIV are thus obtained.

In Chart 4, the lactone XLV is obtained by photoisomerization whereby the latent $C_{13}—C_{14}$ double bond is isomerized from trans to cis. See for example U.S. Patent No. 4,026,909. Compound XXXVIII is irradiated, preferably of wave length about 3500 Angstroms, until an equilibrium mixture of cis and trans isomers is obtained. The progress is conveniently monitored by thin layer chromatography. The mixture is then separated by conventional methods, for example silica gel chromatography. Thereafter the 3'-oxo groups are replaced by Q in the manner described above, and the acyl groups of R_4 are replaced, first with hydrogen, and then with blocking groups R_{10} to form the compounds of formula XLVI.

In Chart 5 the process is directed to lactones of formula LII wherein there is triple bond at latent $C_{13}—C_{14}$. The general procedure follows that of U.S. Patent No. 4,029,681. The formula-XLIX mono-halo compound is obtained by halogenation of XXXVIII to yield XLVII followed by dehydrohalogenation and dehalogenation. The halogenation is conveniently done with a reagent such as N-bromosuccinimide or alternatively, a solution of bromine in carbon tetrachloride. Dedhydrohalogenation proceeds by addition of a base such as pyridine or methanolic sodium acetate. Dehalogenation is achieved with the usual reagents, for example zinc-acetic acid.

Optionally the formula-XLIX mono-halo compound is prepared using lactone XXXVII of Chart 3 and a Witting reagent derived from a 1-halophosphonate. Whereas bromo is shown in Chart 5, chloro derivatives are useful for this procedure.

The formula-L compounds are obtained by replacing the 3'-oxo group with Q, replacing acyl groups at R_{14} with hydrogen, and then blocking hydroxyl groups with R_{10}. Thereafter formula-LI compounds are obtained by dehydrogenation, for example with a strong base such as potassium t-butoxide or sodium methoxide in dimethylsulfoxide or similar aprotic solvent. The formula-LII lactone results from LI on standing with a trace of acid present.

Referring now again to Chart 1, for those compounds in which D is

$$\text{cis}—CH{=}CH—CH_2—(CH_2)_g—\underset{R_{11}}{\overset{R_{10}}{\underset{|}{\overset{|}{C}}}}—$$

the transformati n of VIII to IX and X is shown specifically in Chart 7 in the sequence VIII — LIII — LIV — LV. In Chart 7 step (a) the f rmula-VIII lactone is reduced t lactol LIII and thereafter that lactol is alkylated by the Wittig reaction using an ylid prepared from a phosphonium bromide of the formula

$$(C_6H_5)_3P^+—CH_2CH_2—(CH_2)_g—\underset{\substack{|\\ R_{11}}}{\overset{\substack{R_{10}\\ |}}{C}}—COOH \qquad Br^-$$

in step (b) of Chart 7 to yield LIV. Thereafter in step (c) the $PGF_2\alpha$-type products of formula LV are obtained by replacing blocking groups R_{18} at R_{13} and Q_1 with hydrogen and optionally esterifying the acid. When R_{10} and R_{11} are fluoro, for example, the products are 2,2-difluoro-19,20-didehydro-$PGF_2\alpha$-type compounds.

In Chart 1, the $PGF_2\alpha$-type products with blocking groups represented by formula IX are optionally transformed to PGE_2-type compounds XI using oxidizing agents and conditions which selectively oxidize secondary hydroxy groups to carbonyl groups in the presence of carbon-carbon double bonds. Oxidation r agents known in the art for this purpose include the Jones reagent, i.e. chromic acid, for which see J. Chem. Soc. 39 (1946). Thereafter the formula-XII 19,20-didehydro-PGE_2-type compounds are obtained by deblocking the formula-XI compounds.

The formula-XII 19,20-didehydro-PGE_2-type compounds are also useful for preparing $PGF_2\beta$-type compounds within the scope of formula III by the general method of carbonyl reduction as is known in the art. See for example U.S. Patent No. 3,796,743 or Bergstrom et al. Acta Chem. Scand. 16, 969 (1962). Any reducing agent is used which does not react with carbon-carbon double bonds or ester groups. Preferred reagents are lithium (tri-tert-butoxy) aluminum hydride, the metal borohydrides, e.g., sodium, potassium and zinc borohydrides and metal trialkoxy borohydrides, e.g., sodium trimethoxyborohydride. The mixtures of alpha and beta hydroxy reduction products are separated into the individual alpha and beta isomers by methods known in the art for the separation of analogous pairs of known isomeric prostanoic acid derivatives. See for example, Bergstrin et al., cited above, Granstrom et al., J. Biol. Chem. 240, 457 (1965), and Green et al., J. Lipid Research 5, 117 (1964). Especially pr ferred as separation methods are column or partition chromatography procedures, both normal and reversed phase, preparative thin layer chromatography and countercurrent distribution procedures.

Again following Chart 1, 9-deoxy-9-methylene-19,-20-didehydro-PGE_2 compounds of formula XIV are obtained from the formula-XI compounds using procedures known in the art. See for example U.S. Patent No. 3,950,363, applying the procedure of C. A. Johnson et al., J. Am. Chem. Soc. 95, 6462 (1973). Here the carbanion of a sulfoximine of the formula

$$O{=}\underset{\substack{\|\\ CH_3}}{\overset{\substack{C_6H_5\\ \|}}{S}}{=}N—CH_3$$

g nerated, for example, with an alkyllithium or an alkylmagnesium halide, is reacted with the formula-XI compound to form a sulfonimidoyl adduct of formula LVI.

Thereafter reductive elimination with, for example aluminum amalgam in the presence of acids such as acetic acid or hydrochloric acid yields the formula-XIV products, generally free of the blocking groups. If formula-XIII compounds are present they are readily hydrolyzed in the known way to remove blocking groups R_{10}.

Other formula-III 19,20-didehydro compounds within the scope of D are prepared by the processes of charts 8—15. When D is cis-CH_2—CH=CH—CH_2—CH_2—, reference is made to chart 8. See also U.S. Patent No. 3,933,889. Lactol LIII is transformed to enol ether LVII, for example by reaction with hydrocarbyloxymethylenetriphenylphosphorane of the formula $(C_6H_5)_3P{=}CH—OR_{17}$, although R_{17} is preferably alkyl of one to 4 carbon atoms, inclusive. See, for example, S. G. Levine, J. Am. Chem. Soc. 80, 6150 (1958). The reagent is conveniently prepared from a corresponding quaternary phosphonium halide and a base, e.g. butyllithium or phenyllithium at a low temperature, such as below −10°C. Methoxymethylene-triphenylphosphonium chloride is particularly useful. Various other hydrocarbyloxymethylenetriphenylphosphoranes are useful for preparing the formula-LVII intermediates, wherein R_{17} is hydrocarbyl, including alkoxy (of 1 to 4 carbon atoms)-, aralkoxy-, cycloalkoxy-, and aryloxymethylenetriphenylphosphoranes. Examples of these hydrocarbyloxymethylenetriphenylphosphoranes are 2-methylbutoxy-, isopentyloxy-, heptyloxy-, octyloxy-, nonyloxy-, tridecyloxy-, octadecyloxy-, benzyloxy-, phenethyloxy-, p-methylphenethyloxy-, 1-methyl-3-phenylpropoxy-, cyclohexyloxy-, phenoxy-, and p-methylphen xymethylenetriphenyl-phosphorane. See for example Organic Reactions Vol. 14, pages 346—348, John Wiley and Sons, Inc., N.Y. (1965).

C nsider next step (b) of Chart 8 wherein the formula-LVII enol ether intermediates are hydrolyzed to the formula-LVIII lact ls. This hydrolysis is done under acidic conditions for example with perchloric acid or acetic acid in tetrahydr furan. Reaction temperatures of 10°C. to 100°C. may be employed.

Finally in step (c) of Chart 8, the formula-LIX compounds are obtained by the Wittig reaction using

th ylid d rived from 3-carboxypropyltriphenylphosphonium halide and sodio methylsulfinylcarbanide. Dimethyl sulfoxide is conveniently used as a solvent, and the reaction may be done at about 25°C. Thereaft r the blocking groups are r moved by mild acid hydrolysis to yield the Δ^4 products of formula LIX.

19,20-didehydro compounds of formula III wherein D is $-(CH_2)_3-(CH_2)_0-CH_2-$ are prepared by th process of Chart 9. The none compound LX is available by the steps of Chart 10. In Chart 10 the starting compound is a lactone of formula VIII blocked at R_{13} and Q_1, for which see the same formula-VIII compound discussed above for chart 1 and related charts 2—5. In step (a) of Chart 10 the triol acid of formula LXVIII is formed by hydrolysis, opening the lactone ring. The hydrolysis occurs in a solvent containing water, for example, in methanol, dioxane, or tetrahydrofuran, in the presence of a base, such as an alkali metal hydroxide or carbonate, preferably sodium hydroxide. The reaction occurs in the range of about 0° to 100°C. and is conveniently done at ambient conditions. In this, as in all steps described herein, the duration of the reaction is determined most readily by following it with TLC. During this step the blocking groups R_{15} are not removed.

In step (b) silylated compound LXIX is obtained from LXVIII by procedures known in the art or described herein. See, for example, Pierce, "Silylation of Organic Compounds", Pierce Chemical Co., Rockford, Illinois (1968). The necessary silylating agents for these transformations are known in the art or are prepared by methods known in the art. See, for example, Post, "Silicones and Other Organic Silicon Compounds", Reinhold Publishing Corp., New York, N.Y. (1949). These reagents are used in the presence of a tertiary base such as pyridine at temperatures in the range of about 0° to +50°C.

Alternately, a chlorosilane is used with a corresponding disilazane.

Although a wide variety of silylating agents are available, it is preferred that the silyl groups on the ring contain at least one hindered group, for example:

isopropyl,
secondary butyl,
tert-butyl,
cyclohexyl, or
phenyl.

The silyl groups with hindered substituents are characterized as being less susceptible to hydrolysis than, for example, trimethylsilyl, and therefore resistant to replacement during subsequent steps, particularly step (d). Examples of preferred silyl groups for the cyclopentane ring are:

isopropyldimethylsilyl,
sec-butyldimethylsilyl,
tert-butyldimethylsilyl,
triisopropylsilyl,
cyclohexyldimethylsilyl, and
triphenylsilyl.

In addition to the silylation methods discussed above, it is advantageous to silylate with a chlorosilane in the presence of imidazole in a solvent such as dimethylformamide. See Corey et al., J. Am. Chem. Soc. 94, 6190 (1972). The temperature range for the reaction is about −10° to +80°C.

In step (c) the formula-LXX compound is obtained by selective hydrolysis of silyl from the terminal carboxyl group. Generally an alkali metal carbonate is employed in water and a cosolvent such as methanol, tetrahydrofuran or dioxane, in a temperature range of about −10° to +100°C. If the silyl group on the ring is hindered, a stronger base such as sodium hydroxide may be used to selectively remove the silyl group from the carboxyl.

In step (d), oxidative decarboxylation is employed to yield the formula-LXXI compound. See J. D. Bacha and J. K. Kochi, Tetrahedron, 24, 2215 (1968). Compound LXX is treated in solution, for example in benzene, toluene, xylene, or heptane, with a copper (II) salt such as the acetate, chloride, or nitrate, solubilized with a compound such as pyridine, followed by a lead (IV) salt such as the acetate or benzoate. Decarboxylation may be done either thermally (60—100°C.) or photochemically using radiation of about 3000—3700 Å as from mercury vapor lamps, in a temperature range of about 0° to 60°C.

In step (e), the compound of formula LXXII is obtained by selective hydrolysis of the silyl groups without removing the R_{10} blocking groups. For this purpose a base is used in a liquid medium such as dioxane r tetrahydrofuran. For unhindered silyl groups an alkali metal carbonate is useful; for hindered groups, such as dimethyl-t-butylsilyl, a tetra-n-alkylammonium fluoride such as tetra-n-butylammonium fluoride is preferred, in a temperature range of −10° to +50°C. See E. J. Corey et al., J. Am. Chem. Soc. 94, 6190 (1972).

In step (f) the formula-LX ketone is obtained by oxidation. Useful for this purpose is pyridinium chlorochr mate. Collins reagent, and especially Jones reagent at about −40°C. to about 25°C. See J.

Chem. Soc. 39 (1946). Ac ton is a suitable diluent for this purpose, and a slight exc ss beyond th amount necessary to oxidize th hydr xy groups of the reactant is used.

Referring again to Chart 9, step (a), compound LXI is obtained by conjugativ addition with a lithium diaryl cuprate reactant prepared from

$$Br{-}(CH_2)_3{-}(CH_2)_g{-}\overset{\displaystyle R_{10}}{\underset{\displaystyle R_{11}}{C}}{-}CH_2{-}O{-}Si(A)_3$$

wherein $Si(A)_3$ is as defined above. For the synthesis of a cuprate reagent see, for example, Posner, Org. React. 19,1 (1972) and Normant, Synthesis 63 (1972). See also Posner for typical conditions for addition to an enone.

It is conveniently done in a solvent such as diethyl ether or tetrahydrofuran at about −78°C. to 0°C. A related addition has been reported by Stork et al., J. Am. Chem. Soc. 97, 4745 (1975).

In step (b) compound LXII is obtained by reduction of the ketone, using methods known in the art, for example with sodium borohydride at about 0°C. or lithium tri(sec-butyl)borohydride. The reduction yields both 9α and 9β hydroxy epimers which are separated, for example by silica gel chromatography.

In step (c) the formula-LXIII compounds are obtained from the formula-LXII compounds above by blocking free hydroxyls with R_{18} carboxyacyl groups. For example, R_{18} may represent an aromatic group such as benzoyl, substituted benzoyl, mono-esterified phthaloyl, naphthoyl and substituted naphthoyl, or an aliphatic group such as acetyl or pivaloyl. For introducing those blocking groups, methods known in the art are used.

Thus, an aromatic acid of the formula $R_{18}OH$, wherein R_{18} is an aromatic group within the scope of R_{12} as defined above, for example benzoic acid, is reacted with the formula-LXII compound in the presence of a dehydration agent, e.g. sulfuric acid, zinc chloride, or phosphoryl chloride; or an anhydride of the aromatic acid of the formula $(R_{18})_2O$, for example benzoic anhydride, is used.

Preferably, however, an aromatic acyl halide, for example benzoyl chloride, is reacted with the formula-LXII compound in the presence of a tertiary amine such as pyridine, triethylamine, and the like. The reaction is carried out under a variety of conditions using procedures generally known in the art. Generally, mild conditions are employed, e.g. 20—60°C., contacting the reactants in a liquid medium, e.g. excess pyridine or an inert solvent such as benzene, toluene or chloroform. The acylating agent is used either in stoichiometric amount or in excess. There may be employed, therefore, benzoyl chloride, 4-nitrobenzoyl chloride, 3,5-dinitrobenzoyl chloride, and the like, i.e. $R_{18}Cl$ compounds corresponding to the above R_{18} groups. If the acyl chloride is not available, it is made from the corresponding acid and phosphorus pentachloride as is known in the art.

Aliphatic carboxyacylating agents useful for this transformation are known in the art or readily obtainable by methods known in the art, and include carboxyacyl halides, preferably chlorides, bromides or fluorides, and carboxyacid anhydrides. The preferred reagent is an acid anhydride. Examples of acid anhydrides useful for this purpose are

acetic anhydride,
propionic anhydride,
butyric anhydride,
pentanoic anhydride,
nonanoic anhydride,
tridecanoic anhydride,
stearic anhydride,
(mono, di, or tri)chloroacetic anhydride,
3-chlorovaleric anhydride,
3-(2-bromoethyl)-4,8-dimethylnonanoic anhydride,
cyclopropaneacetic anhydride,
3-cycloheptanepropionic anhydride,
13-cyclopentanetridecanoic anhydride,
phenylacetic anhydride,
(2 or 3)-phenylpropionic anhydride,
13 phenyltridecanoic anhydride, and
phenoxyacetic anhydride.

In step (d) the formula-LXIII compounds are deblocked at C-1 to yi ld the formula-LXIV alcohols, by selective hydrolysis without r moving blocking groups R_{18} and R_{10}. For example, if $-Si(A)_3$ is tert-butyldimethylsilyl, tetra-n-butylammonium florid is mploy d.

In step (e) the formula-LXV compounds ar obtain d by xidizing the terminal C-1 hydroxyl groups of LXIV to carb xyl groups using methods described h r in r known in the art.

In st p (f) the f rmula-LXVI compounds are obtained by sel ctiv hydrolysis of the blocking groups, using bas hydrolysis to replace acyl blocking groups R_{10}. For exampl aqueous potassium hydroxid is useful at about 25—100°C.

Finally in st p (g) th formula-LXVII PFG$_1$-typ products ar obtained by removing th R_{16} blocking groups by mild acid hydrolysis.

The formula-LXVI compounds are useful f r pr paring PGE$_1$-type product following Chart 1.

19,20-didehydro compounds of formula III wherein D is trans-$(CH_2)_3$—CH=CH— are prepared by the process of Chart II. The starting materials of formula LXXIII are available, for example by esterifying the formula-LXVI compounds of Chart 9 and silylating at C-9. For background in preparing Δ^2-prostaglandin analogs, see for example U.S. Patent No. 4,024,174.

In step (a), selenylation is achieved by first forming 2-lithium derivatives of the formula-LXXIII compounds for example by reaction with a lithium amide formed from a secondary amine such as N-isopropylcyclohexylamine. Thereafter the formula-LXXIV compounds are obtained by reaction with diphenyldiselenide or benzeneselenyl bromide using about 3 equivalents for each molecular equivalent of the C-2 lithium derivative at about −78°C.

In step (b) the formula-LXXV $\Delta 2$ compounds are formed by oxidative elimination, for example with hydrogen peroxide or sodium periodate.

In steps (c) and (d) the blocking groups are removed stepwise. Intermediate LXXVI is useful for preparing Δ^2-PGE$_1$ compounds.

Compounds of formula III wherein D is —$(CH_2)_i$—O—$(CH_2)_p$— including —$(CH_2)_3$—O—CH_2—, —$(CH_2)_2$—O—$(CH_2)_2$—, and —CH_2—O—$(CH_2)_3$—, are prepared by the process of Chart 12. The starting materials of formula LX are available from the steps of Chart 10, above. In step (a) compound LXXVIII is obtained by conjugative addition with a lithium diaryl cuprate reactant prepared from

$$Br—(CH_2)_i—O—(CH_2)_p—CH_2—O—Si(A)_3$$

following the general procedure for Chart 9 above. Likewise steps (b) through (g) follow the procedures for Chart 9 described above, but proceeding here through intermediates LXXIX, LXXX, LXXXI, LXXXII, and LXXXIII to 3-, 4-, or 5-oxa-PGF$_1\alpha$ products represented by formula LXXXIV.

The 5-oxo-PGF$_1\alpha$ products are alternatively prepared by the steps of Chart 13 which yield LXXXVII. Starting materials are lactols LIII, for which see Chart 7 above. Step (a) yields alcohol LXXXV on reduction with aqueous methanolic or ethanolic sodium borohydride. Alternatively the predecessor lactone VIII of Chart 7 is reduced in one step to LXXXV for example with lithium aluminum hydride or diisobutylaluminum hydride at 0—35°C. In step (b) the Williamson synthesis yields the formula-LXXXVI intermediates by reaction with a halobutyrate of the formula

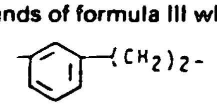
$$Hal—(CH_2)_3—COOR_0$$

or an orthoester of the formula

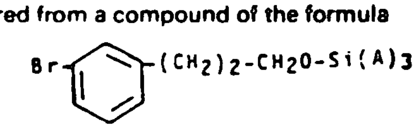
$$Br—(CH_2)_3—C(OR_8)_3.$$

For background see U.S. Patent No. 3,931,279, column 35. Finally in step (c) product LXXXVII is obtained by removing blocking groups R_{15} by acid hydrolysis in the usual manner.

Inter-phenylene 19,20-didehydro compounds of formula III wherein D is



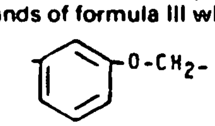
are prepared by the process of Chart 14. The starting materials of formula LX are available from the steps of Chart 10, above. In step (a) compound LXXXVIII is obtained by conjugative addition with a lithium diaryl cuprate reactant prepared from a compound of the formula



following the general procedure for Chart 9 above. Thereafter steps (b) through (g) follow the procedures for Chart 9, described above, but proceeding through intermediates LXXXIX, XC, XCI, XCII, and XCIII to the inter-phenylene end products XCIV.

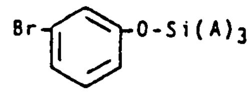
Th formula-XCIII compounds re useful for preparing PGE$_1$-type products following Chart 1.

Oxa-ph nylene 19,20-didehydro compounds of formula III wher in D is



are prepared by the process of Chart 15. Here again the formula-LX starting materials are available from

th steps of Chart 10 above. In step (a) compound XCV is obtain d by conjugative additi n with a lithium diaryl cuprate reactant prepared from a compound of th formula



following the g neral procedur for Chart 9 above. Steps (b), (c), and (d) follow the procedures for similar steps (b), (c), and (d) in Chart 9 described above, but proceeding through intermediates XCVI, XCVII, and XCVIII. In step (e) the Williamson synthesis yields the formula-XCIX intermediate by reaction with a haloacetate of the formula

$$Hal—CH_2—COOR_9$$

or an orthoester of the formula

$$Br—CH_2—C(OR_9)_3.$$

In step (f) compound C is obtained by selective hydrolysis of the acyl blocking groups, using base hydrolysis and in step (g) the R_{18} blocking groups are removed by mild acid hydrolysis to yield CI.

The formula-C compounds are useful for preparing PGE_1-type products following Chart 1.

Referring to formula III for the 19,20-didehydro compounds disclosed herein, the preparation of compounds within the scope of D, Q, R_2, R_3, R_4, W, and X as defined herein has been discussed above and illustrated by Charts 1—15. Still other transformations may be accomplished by chemical processes which are known to those skilled in the art.

Charts 1—15 are generally shown to yield the acid form of the products. If a PGE-type product is obtained as an ester, the acid form is prepared by enzymatic hydrolysis using an esterase enzyme composition obtained from *Plexaura homomalla* (Esper) 1792, for which see U.S. Patent No. 3,840,434, October 8, 1974. If, as in Chart 11, a lower alkyl ester of a PGF_1-type intermediate or product is obtained, that ester is readily converted to the acid form by saponification. The acid is then used to prepare various esters of formula III within the scope of R_8 by methods known in the art. For example, the alkyl, cycloalkyl, and aralkyl esters are prepared by interaction of said acids with the appropriate diazohydrocarbon. For example, when diazomethane is used, the methyl esters are produced. Similar use of diazoethane, diazobutane, 1-diazo-2-ethylhexane, diazocyclohexane, and phenyldiazomethane, for example gives the ethyl, butyl, 2-ethylhexyl, cyclohexyl, and benzyl esters, respectively. Of these esters, the methyl or ethyl are preferred.

Esterification with diazohydrocarbons is carried out by mixing a solution of the diazohydrocarbon in a suitable inert solvent, preferably diethyl ether, with the acid reactant, advantageously in the same or a different inert diluent. After the esterification reaction is complete, the solvent is removed by evaporation, and the ester purified, if desired, by conventional methods, preferably by chromatography. It is preferred that contact of the acid reactants with the diazohydrocarbon be no longer than necessary to effect the desired esterification, preferably about one to about ten minutes, to avoid undesired molecular changes. Diazohydrocarbons are known in the art or can be prepared by methods known in the art. See, for example Organic Reactions, John Wiley & Sons, Inc., New York, N.Y. Vol. 8, pp. 389—394 (1954).

An alternative method for esterification of the carboxyl moiety of the acid compounds of formula III comprises transformations of the free acid to the corresponding silver salt, followed by interaction of that salt with an alkyl iodide.

The phenyl and substituted phenyl esters of the formula III compounds are prepared by silylating the acid to protect the hydroxy groups, for example, replacing each —OH with $—O—Si—(CH_3)_3$. Doing that may also change —COOH to $—COO—Si—(CH_3)_3$. A brief treatment of the silylated compound with water will change $—COO—Si(CH_3)_3$ back to —COOH. Procedures for this silylation are known in the art and are available. Then, treatment of the silylated compound with oxalyl chloride gives the acid chloride which is reacted with phenol or the appropriate substituted phenol to give a silylated phenyl or substituted phenyl ester. Then the silyl groups, e.g., $—O—Si—(CH_3)_3$ are changed back to —OH by treatment with dilute acetic acid. Procedures for these transformations are known in the art.

A preferred method for substituted phenyl esters is that disclosed in U.S. Patent No. 3,890,372 in which a mixed anhydride is reacted with an appropriate phenol or naphthol. The anhydride is formed from the acid with isobutylchloroformate in the presence of a tertiary amine.

Phenacyl-type esters are prepared from the acid using a phenacyl bromide, for example p-phenylphenacyl bromide, in the presence of a t rtiary amine. See for example U.S. Patent No. 3,984,454, German Offenlag. 2,535,693, and D rwent Farmdoc N . 16828X.

Charts 16—20 r lat t transformati ns at C-1 for these 19,20-didehydr compounds.

When a 2-decarboxy-2-hydroxymethyl product is d sired, i.e., when R_1 is $—CH_2OH$, the acid r lower alkyl ester form of III is reduced (see Chart 16 CII to CIII) using reagents known t reduce carboxylic acids to corresponding primary alcohols. See for example U.S. Patent No. 4,028,419, as to lithium aluminum hydride r diisobutylaluminum hydride. Useful s lvents include diethyl ether,

tetrahydrofuran or dimethoxyethan . The reaction may b run at −78°C to 100°C, although preferably at about 0°C . to 50°C. Other carbonyl groups in the mol cul will also be reduced unless suitably protected as oximes, k tals, or similar carbonyl derivatives which are readily restored to carbonyls after th r duction has be n accomplished.

A 2-decarboxy-2-hydroxym thyl-PGE type compound may also be prepared by blocking th C-1 alcohol groups as shown in Chart 16, formula CV. Thereafter the C-9 hydroxy is oxidized to form CVI and finally the $-Si(A)_3$ blocking group is removed by hydrolysis. It is preferred that $-Si(A)_3$ be tert-butyl-dimethylsilyl.

Compounds in which R_1 is

$$-CH_2-N(R_7)(R_8) \text{ or } -\overset{\overset{\displaystyle O}{\|}}{C}-N(R_7)(R_8)$$

are conveniently prepared from the formula-III products which are acids, i.e. R_1 is —COOH. For background see U.S. Patent No. 4,085,139. PGF-type compounds or 9-methylene compounds are simply converted to a mixed anhydride using an alkyl, aralkyl, phenyl, or substituted phenyl chloroformate in the presence of a tertiary amine. A preferred reagent is isobutylchloroformate.The anhydride is then reacted with ammonia or the appropriate amine $(R_7)(R_8)NH$ to form the amide wherein R_1 is

$$-\overset{\overset{\displaystyle O}{\|}}{C}-N(R_7)(R_8).$$

The 2-decarboxy-2-aminomethyl compound is prepared from the amide by carbonyl reduction using methods known in the art, for example lithium aluminum hydride reduction. PGE-type compounds are obtained by oxidation of the PGF-type compounds preferably when the terminal amine group is in the form of an amine salt.

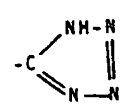
In Chart 17 is shown an alternate procedure for the amine-terminated PGE-type compounds. The starting material of formula CVIII is obtained from a formula-III 19,20-didehydro PGE-type compound by ketalization with ethylene glycol. For background see, for example, M. J. Cho et al., J. Medicinal Chem. 20, 1525 (1977). Anhydride CIX is formed in step (a), amide CX in step (b), and amine CXI in step (c). Finally in step (d) the ketal is hydrolyzed to the PGE-type product CXII by methods known in the art. See also U.S. Patent No. 3,915,994.

Compounds in which R_1 is

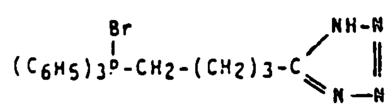
$$-\overset{\overset{\displaystyle O}{\|}}{C}-NH-SO_2-R_{20}$$

i.e. the N-sulfonylamides, are prepared from the formula-III compounds in their acid form. In Chart 18 are shown the steps by which those compounds, represented by formula CXIII, are transformed to the sulfonylamides of formula CXV. In step (a) the acid is converted to a mixed anhydride, here shown as CXIV, by reaction with isobutylchloroformate in the presence of a tertiary amine such as triethylamine. Other mixed anhydrides are also useful. In step (b) the anhydride is then reacted with the sodium derivative of a sulfonylamide of the formula $Na-NH-SO_2-R_{20}$ obtained for example by reaction of methanolic sodium methoxide with an equimolar amount of the sulfonylamide. The reaction of step (b) is promoted by the addition of a small amount of hexamethylphosphoramide to insure homogenity.

Compounds in which R_1 is



are obtained by either the process of Chart 19 or Chart 20. In Chart 19 the starting lactone LIII is available above, for example see Chart 7. Applying the Wittig reaction and using the ylid prepared from a phosphonium compound of the formula



the formula-CXVI compound is obtained. S e U.S. Patent No. 3,928,391. Replacem nt f blocking groups R_{19} then yields the products of f rmula CXVII. Optionally the CXVI compounds are transformed by methods disclosed h rein or known in the art to other tetraz lyl compounds, e.g. PGE-type compounds, within the scope of formula III.

In Chart 20 th proc ss goes stepwise from an amide to a nitrile t a tetrazolyl c mpound. The starting mat rials CXVIII ar available h rein, for example from an acid blocked preferentially with R_{10} at

C—11 and C—15 and converted to an amide by way of a mix d anhydride, then blocked with silyl groups at C—9.

In step (a) the formula-CXIX nitrile is prepared by dehydration f amide CXVIII with a carbodiimide Se C. R ssler et al., J.Org. Chem. 26, 3354 (1961). For xampl , N.N'-dicyclohexylcarbodiimide (DCC) is us ful in pyridin at about room temp rature.

In step (b) the tetrazolyl group in CXX is formed from the above nitrile by reaction with sodium azide and ammonium chloride in a medium such as dimethylformamide. See "Heterocyclic Compounds", R. C. Elderfield, ed., John Wiley and Sons, Inc., N.Y., Vol. 8, pages 11—12.

In steps (c) and (d) the blocking groups —$Si(A)_3$ and R_{10} are replaced by desilylation and mild acid hydrolysis in the usual manner to yield CXXI and then CXXII. Compound CXXI is useful as an intermediate for preparing other tetrazolyl compounds including PGE-type products within the scope of formula III.

In Chart 21 is shown a preferred route to the 15-alkyl compounds of formula LV. In step (a) intermediate CXXIV is formed by the Grignard reaction on CXXIII using R_0MgHal or trialkylaluminum (see E. W. Yankee et al., J. Am. Chem. Soc. 96, 5865 (1974) and references cited therein). Starting material CXXIII is readily available, for example from XXXVIII of Chart 3 by steps disclosed herein or known in the art. Steps (b), (c), and (d) correspond to Chart 7, steps (a), (b), and (c) except that there need not be a blocking group at the 3' position. Products LV, mixed C—15 epimers, are separated into the 15S and 15R forms, for example by silica gel chromatography, preferably in the form of their methyl esters. The free acids are readily obtained by saponification of the methyl ester with mild alkaline conditions.

Included in the 19,20-didehydro compounds of formula III are the pharmacologically acceptable salts when R_6 is a cation. Such pharmacologically acceptable salts useful for the purposes described above are those with pharmacologically acceptable metal cations, ammonium, amine cations, or quaternary ammonium cations.

Especially preferred metal cations are those derived from the alkali metals, e.g. lithium, sodium and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron are within the scope of this invention.

Pharmacologically acceptable amine cations are those derived from primary, secondary, or tertiary amines.

Salts containing pharmacologically acceptable cations are prepared from the final formula-III compounds in free acid form, i.e. wherein R_1 is —COOH, by neutralization with appropriate amounts of the corresponding inorganic or organic base, examples of which correspond to the cations and amines listed above. These transformations are carried out by a variety of procedures known in the art to be generally useful for the preparation of inorganic, i.e., metal or ammonium salts, amine acid addition salts, and quaternary ammonium salts. The choice of procedure depends in part upon the solubility characteristics of the particular salts to be prepared. In the case of the inorganic salts, it is usually suitable to dissolve the formula-III acid in water containing the stoichiometric amount of a hydroxide, carbonate, or bicarbonate corresponding to the inorganic salt desired. For example, such use of sodium hydroxide, sodium carbonate, or sodium bicarbonate gives a solution of the sodium salt. Evaporation of the water or addition of a water-miscible solvent of moderate polarity, for example, a lower alkanol or a lower alkanone, gives the solid inorganic salt if that form is desired. Amine and quaternary ammonium salts are prepared by similar methods using appropriate solvents.

19-Hydroxy Prostaglandin Compounds

This second section will disclose the procedures for preparing the formula-III 19-hydroxy prostaglandin compounds and intermediates illustrated by Charts 22—28.

Referring to Chart 22, there is shown a simple method of forming (19R, S)-19-hydroxy-PGF's, i.e., mixed 19R and 19S isomers. The 19,20-didehydro-PGF compounds of formula CXXVII are available by the methods described in the section above. The olefin is hydrated by oxymercuration-demercuration using mercuric acetate and sodium borohydride for which see Fieser et al., Reagents for Organic Syntheses, Vol. II, 1969, p. 265. The oxymercuration is done conveniently at about 25°C., after which the mercury is removed by reduction with sodium borohydride, preferably at below 10°C. to minimize side reactions.

In Chart 23, (19R,S)-19-hydroxy prostaglandin compounds are also made by the processes disclosed, but here the approach is through a (19R,S)-19-hydroxy lactone of formula CXXIX. The formula-VIII 19,20-didehydro starting lactones are available by the methods described in the section above. Oxymercurati n-dem rcurati n in step (a) foll wed by blocking with R_{10} in step (b) then yields CXXIX, which is c nverted t CXXX and CXXXI by m thods known in the art or described herein. The PGE-type compounds of formula-CXXXIII are obtained by oxidizing the formula-CXXX compounds at C—9 to form CXXXII, thereafter removing blocking groups.

Chart 24 illustrates the preparation of other (19R,S)-19-hydroxy compounds, including 2-decarboxy-2-hydroxymethyl compounds f formulas CXLII, CXLIV, and CXLV. Chart 24 illustrates the reduction of carboxylic esters to the hydroxymethyl function and also the reduction of ethylenic unsaturation at C—5 and C—13. The formula-CXXXIV 19,20-didehydro starting materials are available

fr m methods describ d in the section above. S e for xampl th corresponding acids LIV of Chart 7 which ar r adily sterified to th se lower alkyl est rs.

In step (a) the silylat d compound CXXXV is formed by th usual silylation r acti ns, for which see the d scription for Chart 9 abov . Of th various silyl groups, dimethyl-t-butylsilyl is pr ferred. In step (b) th terminal olefinic groups is hydrated by oxym rcuration-d m rcurati n to yi ld the mixed (19R)- and (19S)-19-hydroxy isomers. In step (c) catalytic hydrog nation over palladium yields a mixture f the $PGF_1\alpha$ and 13,14-dihydro-$PGF_1\alpha$ compounds, indicated in formula CXXXVII by a solid and a broken line at C_{13}—C_{14}. In step (d), 19-hydroxyls are blocked, for example with THP. In step (e) the ester is reduced to carbinol CXXXIX using for example, lithium aluminum hydride. In step (f) the newly-formed hydroxyls are blocked, for example with THP. In step (g) the CXL compounds are desilylated to the CXLI compounds, for example with a tetra-n-alkylammonium fluoride as described above for Chart 9. In step (h) deblocking, as in dilute acid, yields the PGF-type compounds of formula CXLII which are separated by silica gel chromatography. In step (i) the blocked PGF-type compounds CXLI are oxidized by the usual methods to the CXLIII PGE-type compounds which are deblocked and separated in step (j) to yield CXLIV and CXLV.

If only the PGF-type compounds of formula CXLII are desired, the process is simplified according to Chart 25. In step (a) the 19,20-didehydro starting material CXLVI is hydrated by oxymercuration-demercuration to yield CXLVII. Catalytic hydrogenation then yields CXLVIII, together with the 13,14-dihydro compound. CXLVIII is separated and reduced to CXLIX with lithium aluminum hydride and finally in step (d) the blocking groups are replaced with hydrogen using mild acid hydrolysis.

19-Hydroxy compounds having specific configuration at C-19 are obtained in several ways. Chart 26, herein, illustrates the use of a Grignard reagent prepared from one of the isomers of CLI. For details on the resolution of the (±)-1-penten-4-ol as its phthalate ester via the brucine salt see J. C. Sih, Prostaglandins, Vol. 13, No. 5, pp. 831—835 (1977). The starting material XXVI is available, for which see the discussion above for Chart 2. In step (a) the formula-CLII lactone is readily obtained using the Grignard reagent identified above. Other formula-CLIII lactones having the various forms of Q, are prepared by methods known in the art including blocking, or, when Q_1 includes 3'-alkyl substitution, forming the 3'-oxo compound by oxidation thereafter applying the Grignard reaction as for Chart 2 above.

Chart 27 shows the steps for forming other lactones, which together with the formula-CLIII lactones of Chart 26 above are useful for preparing 19-hydroxy prostaglandins by the processes of Chart 28.

In Chart 27, the formula-XXXVII starting aldehydes are available, as shown above for Chart 3. In step (a) the Wittig reaction is employed using the ylid derived from a phosphonate of formula CLXI. In preparing 19-hydroxy end products having specific configuration at C—19 the appropriate optically active isomer of CLXI is used. Preferably that isomer is used which yields an end product having highest pharmacological activity as determined by standard biological tests.

Various methods are available for obtaining optically active isomers of CLXI. Preferably the phosphonate is prepared from dimethyl methylphosphonate and an optically active methyl ester of a corresponding 5-hydroxy-hexanoic acid, suitably blocked with R_{18}. Such hexanoic acids are available in resolved state by application of the phthalate ester-brucine salt procedure of Sih cited above. Thus, for example the methyl ester of 5-hydroxy-hexanoic acid is esterified with phthalic acid and the half-ester thus formed is resolved via its brucine salt by fractional crystallization. Thereafter the acid is recovered and converted to the methyl ester and thence to the phosphonate. Other 2-substituted-5-hydroxy-hexanoic acids are known or available to those skilled in the art. For example when R_3 and R_4 are methyl, the methyl ester of 2,2-dimethyl-5-oxo-hexanoic acid is reduced. When R_3 and R_4 are fluoro, the methyl ester of 5-hydroxy-2-oxo-hexanoic acid is fluorinated, for example with molybdenum hexafluoride-boron trifluoride. See U.S. Pat. No. 3,962,293. These acids are resolved in the same manner as described above and thereafter converted to phosphonates.

Still another method of obtaining the optically active 5-hydroxy-hexanoic acids is by starting with an optically-active ω-halopentan-2-ol, for example Br—$(CH_2)_3$—CH(OH)—CH_3, blocking the hydroxyl for example with THP, then forming a Grignard reagent and reacting it with carbon dioxide following Organic Synthesis, Coll. Vol. 1, 2nd ed., 1948, H. Gilman, editor, John Wiley, N.Y.

Continuing with Chart 27, in steps (b), (c), and (d), the 3'-oxo group of CLIV is reduced, the R_{10} carboxyacyl blocking groups are replaced first with hydrogen and then with R_{10} blocking groups, and all other free hydroxyl groups such as at Q are also blocked to yield the formula-CLVI intermediate. Conversion of the trans-CH=CH— olefinic group to cis-CH=CH—, to acetylenic —C≡C—, or to ethylenic —CH_2CH_2— is accomplished by adaptation of the procedures discussed above for Charts 3, 4, and 5.

In Chart 28 the steps leading to products CLXIV, CLXVI, and CLXVIII ar sh wn. The starting mat rials CLXII include CLIII of Chart 26 and CLVI, CLVII, CLVIII, and CLIX of Chart 27, and the general procedur s described above for Chart 1 ar used.

19-Keto Prostaglandin Compounds

This third section will disclose the procedures for preparing th formula III 19-k to prostaglandin compounds illustrat d by Charts 29—33.

Referring to Chart 29, the formula-CXXXVI 19-hydroxy compounds of Chart 24 are oxidized to 19-k t compounds. Suitable blocking at C—9, C—11, and C—15 hydroxyls protects those hydroxyls from xidation wh n preparing 19-keto-PGF-type compounds of formula CLXX. In preparing 19-ket -PGE-type compounds of formula CLXXIII, both C—9 and C—19 hydroxy groups are preferably oxidized in one step, using for example the Jones Reagent at about −35°C.

Chart 30 shows a series of similar reactions for preparing the more general compounds of formula CLXXVII and CLXXX. The starting materials of formula IX are available from Chart 1 above. The formula-CLXXV mixed (19R,S) or (±) 19-hydroxy compounds may be replaced with either the (19R) or (19S) compounds available, for example, from Chart 28 above.

Chart 31 shows a sequence of steps for preparing 2-decarboxy-2-hydroxymethyl-19-keto-PGE_1 compounds. The formula-CXLIX starting compounds are available from Chart 25 above. In step (a) the C—1 hydroxy groups are preferentially blocked by silyl. In step (b) the C—9 and C—19 hydroxyls are oxidized, for example with Collins reagent. In step (c) the blocking groups are replaced with hydrogen in the usual way, and the resulting product CLXXXIII and hemiacetal CLXXXIV separated by silica gel chromatography for example. The hemiacetal is converted to the 19-keto compound by mild acid, as in acetic acid-water-tetrahydrofuran.

Chart 32 illustrates a process for broadly-defined 2-decarboxy-2-hydroxymethyl-19-keto-PGE compounds of formula CXCI. The starting materials CLXXXV are readily available, for example by esterification and silylation of CLXXV of Chart 30 above. Procedures for each step have already been described. Thus, for step (a) the reduction of the ester to carbinol CLXXXVI follows that for step (e) of Chart 24. Intermediate CLXXXVIII is also a convenient source of 19-hydroxy products CLXXXIX.

Chart 33 shows steps leading to 2-decarboxy-2-hydroxymethyl-19-keto-PGF compounds of formula CXCVI utilizing previously discussed procedures for each transformation. The starting materials CXCII are readily available, for example by esterification and blocking of IX of Chart 1.

19-Hydroxy-19-methyl Prostaglandin Compounds

This fourth section will disclose the procedures for preparing formula-III 19-hydroxy-19-methyl prostaglandin compounds illustrated by Charts 34—49.

Referring to Chart 34, there are shown the process steps from lactone CXXIX to end products CCI and CCIII.

Starting materials of formula CXXIX are available from Chart 23 above. In step (a) the hydroxyls are oxidized to keto groups, for example with Jones reagent. In step (b) the tertiary carbinol is formed, ither with methylmagnesium halide or trimethylaluminum. Step (c) is the transformation to a lactol and step (d) is Wittig alkylation using an ylid as described above for Charts 1 and 7. Removal of blocking groups yields PGF compounds CCI; oxidation of hydroxyls of CC at C—9 leads to PGE-type compounds CCII and CCIII.

Chart 35 illustrates the transformation of 19-keto compounds in general, suitably blocked, to 19-hydroxy-19-methyl compounds. For the acids, trimethylaluminum in benzene is the preferred reagent in step (a); for esters, the Grignard reagent is useful. The formula-CCV and -CCVII intermediates are useful for making the formula-CCVI, -CCVIII, and -CCX products, applying the general procedures discussed above for Chart 1.

Referring to generic formula III for the 19-hydroxy-19-methyl compounds, other compounds within the scope of D are available not only by the processes of Chart 35 but by the processes of Chart 36—45.

Chart 36 shows the reduction of the olefinic group in the "upper" (carboxy-terminated) side chain. For this purpose hydrogenation in the presence of palladium catalyst is useful. Thereafter products CCXIII and CCXV are obtained.

When D is cis-CH_2—CH=CH—CH_2—CH_2—, the steps of Chart 37 are useful. Lactol CXCIX is available from Chart 34 above. Thereafter steps (a), (b), and (c), following the procedures described above for Chart 8, yield product CCXVIII.

Compounds of formula VI (Δ^2 compounds) wherein D is trans-$(CH_2)_3$—CH=CH— are prepared by the process of Chart 38. Starting materials CCXIX are available from a formula-CCIV compound (Chart 35) wherein D is trimethylene by reduction of the carboxyl group to hydroxymethyl, for example with lithium aluminum hydride. Aldehyde compound CCXX is obtained by oxidation of the —CH_2OH of CCXIX to —CHO, using for example Collins reagent (pyridine —CrO_3) at about 0—10°C. In step (b) the Wittig r action is used, with an ylid obtained from $(CH_3O)_2P(O)CH_2COOH$. See for example Derwent Farmdoc Abstract No. 50715v. Blocking groups are removed in step (c) in the c nventional way to form CCXXII.

Chart 39 repr sents an alternate process to Δ^2 compounds, via selenylati n-deselenylation, applying th procedures described for Chart 11 above. Starting material CCXXIII is available herein, for exampl from CCXII of Chart 36. It is immaterial whether C—19 hydroxyls are blocked or not. Blocking at C—9 may b either with R_{10} or silyl. Accordingly steps (a), (b), and (c) yield products CCXXVI.

The 3- and 4-oxa compounds are obtained by the processes f Charts 40 and 41. These general

procedures are known in the art, see for example U.S. Patent No. 3,944,593. Compounds CCXXXI and CCXXXVIII are formed thereby.

The 5-oxa compounds of formula CCXLI are prepared by the steps of Chart 42. The procedures have been described above for Chart 13.

Inter-phenylene compounds of formula CCL are obtained by the procedures of Chart 43 starting with the intermediates of formula CCXLIII. Those intermediates are shown as the products of Chart 44 starting with lactone CXCVIII of Chart 34 and applying the general procedures of Chart 10 above.

Oxa-phenylene analogs of formula CCLXV are produced by the steps of Chart 45, starting with intermediates CCXLIII and following the general procedures of Chart 15 above.

Where the above processes yield an acid, the esters are prepared by any of the methods described for the 19,20-didehydro compounds above. Likewise esters are transformed to acids by processes known or described herein.

Charts 46—49 relate to transformations at C—1 for these 19-hydroxy-19-methyl compounds.

Formula-CCLXXI 2-decarboxy-2-hydroxymethyl compounds of Chart 46 are obtained by the general procedures described for Chart 16 above.

Amides of formula CCLXXIV and 2-decarboxy-2-amino methyl compounds of formula CCLXXV in Chart 47 are prepared following the general procedures of Chart 17 above. N-Sulfonylamides in which R_1 is

$$-\overset{\displaystyle O}{\overset{\|}{C}}-NH-SO_2O-R_{20}$$

are prepared as described for the 19,20-didehydro compounds above.

Tetrazolyl-terminated compounds of formula CCLXXVIII and CCLXXXII are obtained according to Charts 48 and 49 applying the procedures of Charts 19 and 20 above.

Compounds of formulas IV—VI which are not specifically illustrated or exemplified herein are obtained by transformations using chemical processes disclosed herein or known to those skilled in the art.

For example the transformation of R_6 in Q from hydrogen to methyl at C—15 requires the intermediate 15-oxo compound prepared by oxidation, followed by alkylation with Grignard R_0MgHal or trimethylaluminum, and subsequent separation of the 15α and 15β products, for example by chromatography, preferably of the methyl esters. Preparation of esters and salts and various modifications at C—1, e.g., amides and sulfonamides follow the general procedures discussed for the formula-III 19,20-didehydro compounds.

It should be understood that many of the intermediates disclosed herein are useful not only for the purposes shown but also for many of the above transformations as known in the art.

The products formed from each step of the process are often mixtures, and, as known to one skilled in the art, may be used as such for a succeeding step or, optionally, separated and purified by conventional methods of fractionation, liquid extraction, and the like, before proceeding. It is intended that compounds are claimed not only in their purified form but also in mixtures, for example the formula-IV 19-hydroxy compounds in their mixed (R,S) form.

The invention is further illustrated by, but not limited to, the following examples.

All temperatures are in degrees centigrade.

Infrared absorption spectra are recorded on a Perkin-Elmer model 421 infrared spectrophotometer. Except when specified otherwise, undiluted (neat) samples are used.

The NMR spectra are recorded on a Varian A—60, A—60D, T—60 or XL—100 spectrophotometer in deuterochloroform solution with tetramethylsilane as an internal standard.

Mass spectra are recorded on a Varian Model MAT CH7 Mass Spectrometer, a CEC Model 110B Double Focusing High Resolution Mass Spectrometer, or a LKB Model 9000 Gas Chromatograph-Mass Spectrometer (ionization voltage 22 or 70 ev.) and samples are usually run as TMS (trimethylsilyl) derivatives.

"Brine", herein, refers to an aqueous saturated sodium chloride solution.

"Celite" is a calcium aluminosilicate, useful as a filter aid.

"Collins reagent" is chromium trioxide in pyridine. See Tetrahedron Lett. p. 3363 (1968).

"DIBAL", herein, refers to diisobutylaluminum hydride.

"Florosil", herein, is a chromatographic magnesium silicate produced by the Floridin Co. See Fieser et al., "Reagents for Organic Synthesis" p. 393 John Wiley and Sons, Inc., New York, N.Y. (1967).

"HPLC", herein, refers to high pressure liquid chromatography.

"Jones reagent" is chromic acid, see J. Chem. Soc. p. 39 (1946).

"R_f" herein, refers to the measurement, in thin layer chromatography, of the movement of the sample spot relative to that of the solvent front, on silica gel plates unless specified, and in a solvent system that is identified.

"Skellysolve B", herein, refers to mixed isomeric hexanes.

"THP", her in, r fers to tetrahydropyran-2-yl.

"TLC", h rein, r f rs to thin lay r chromatography.

"Concentrating", as used herein, ref rs to concentration under reduced pressure, preferably at less than 50 mm.and at t mp ratures below 35°C.

"Drying", as used herein, ref rs to contacting a compound, in solution, with an anhydrous agent such as sodium sulfate or magnesium sulfat to rem v water and filtering t r mov solids.

Silica gel chromatography, as used herein, is understood to include elution, collection of fractions, and combination of those fractions shown by TLC to contain the desired product free of starting materials and impurities.

The A—IX solvent system used in thin layer chromatography is made up from ethyl acetate-acetic acid-2,2,4-trimethylpentane-water (90:20:50:100) according to M. Hamberg and B. Samuelsson, J. Biol. Chem. 241, 247 (1966).

Preparation 1 5α-Hydroxy-3α-tetrahydropyran-2-yloxy-2β-(trans-2-formylethenyl)-1α-cyclopentaneacetic Acid, γ-Lactone (Formula XXXVI)

Refer to Chart 6. The title compound is obtained in seven steps starting with the formula-XXIX tricyclic lactone aldehyde, for which see U.S. Patent No.3,816,462.

a. Exo-3-hydroxy-endo-6-vinyl-bicyclo[3.1.0]-hexan-exo-2-acetic acid, γ-lactone (Formula XXX). A solution of the formula-XXIX tricyclic lactone aldehyde (20 g.) in 150 ml. of benzene is treated at 5—10°C. with a solution of the ylid prepared from methyltriphenylphosphonium bromide (54 g.) and 95 ml. of 1.6 M butyllithium in one liter of benzene (previously heated at reflux for one hr. and cooled). The addition is completed within 1—1.5 hr., and, after an additional 0.5 hr. stirring, the mixture is filtered and concentrated. The residue is taken up in 100—200 ml. of ethyl acetate-Skellysolve B (40:60) and left standing to crystallize out the by-product triphenylphosphone oxide. After filtration, the filtrate is subjected to silica gel chromatography, eluting with ethyl acetate-Skellysolve B (40:60). There is obtained the formula-XXX compound, 16.2 g., an oil, having NMR peaks at 1.3—3.0, 4.6—4.9, and 5.0—5.4 δ; and R_f 0.74 (in ethyl acetate-Skellysolve B (50—50)).

b. Endo-6-(1,2-dihydroxyethyl)-exo-3-hydroxy-bi-cyclo[3.1.0]-hexen-exo-2-acetic acid, 3-lactone (Formula XXXI). A solution of the formula-XXX alkene (step a, 8.0 g.) in 80 ml. of acetone is treated with a solution of N-methylmorpholine oxide dihydrate (9.0 g.) in 12 ml. of water, followed by a solution of osmium tetroxide (130 mg.) in 6.5 ml. of t-butanol. When the reaction is completed, the acetone is removed under reduced pressure. The residue is diluted with 100 ml. of water, saturated with ammonium sulfate, and extracted with tetrahydrofuran. The organic phase is dried over magnesium sulfate and concentrated under reduced pressure to yield 12 g. of crude oily product. The oil is subjected to silica gel chromatography to yield the formula-XXXI compound, 8.5 g., an oil, having NMR peaks at 0.7—1 2, 1.3—1 9, 2.4—3.4, 3.4—3 7, 3.7—4.2, and 4.7—5.0 δ; R_f 0.66 (in methanol-dichloromethane (15:85)).

c. 3α-Formylkoxy-5α-hydroxy-2β-(3-propionyloxy-trans-1-propenyl)-1α-cyclopentaneacetic acid, γ-lactone (Formula XXXII). A solution of the formula-XXXI glycol (step b, 7.2 g.) and triethyl orthopropionate (15 g.) in 30 ml. of tetrahydrofuran is treated with 3 μl of trifluoroacetic acid. After one hr. the solvent is removed under reduced pressure and the residue treated with 100 ml. of anhydrous formic acid with stirring. After 15 min. there is added 100 ml. of 1 N. sodium hydroxide and 100 ml. of crushed ice. The mixture is extracted with dichloromethane and the organic phase is washed with 5% aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated. The oil (9.6 g.) thus obtained is subjected to silica gel chromatography, eluting with ethyl acetate-cyclohexane (1:1), to yield the formula-XXXII compound, 4.1 g., having NMR peaks at 1.1, 1.9—3.0, 4.4—4.6, 4.8—5.2, 5.6—5.8, and 8.0 δ; and R_f 0.49 (in ethyl acetate-cyclohexane (1:1)).

d. 3α, 5α-Dihydroxy-2β-(3-propionyloxy-trans-1-propenyl)-1α-cyclopentaneacetic acid, γ-lactone (Formula XXXIII). A solution of the formula-XXXII formate (step c, 4.1 g.) in 35 ml. of dry methanol is treated with sodium bicarbonate (0.5 g.). When the reaction is finished in about 2—3 hr., the solvent is removed under reduced pressure. The residue is partitioned between water and dichloromethane, and the organic phase is dried over magnesium sulfate and concentrated. The oily residue is subjected to silica gel chromatography, eluting with ethyl acetate to yield the formula-XXXIII compound, 2.8 g., having NMR peaks at 1.13, 3.7—4.3, 4.3—4.7, 4.7—5.2, and 5.5—5.8 δ; and R_f 0.65 (in ethyl acetate).

e. 3α-Tetrahydropyran-2-yloxy-5α-hydroxy-2β-(3-propionyloxy-trans-1-propenyl)-1α-cyclopentaneacetic acid, γ-lactone (Formula-XXXIV). A solution of the formula-XXXIII 5-hydroxy lactone (st p d, 2.8 g.) in 10 ml. of dichl rom than is treated with 5 ml. of dihydropyran and 5 mg. of p-toluen sulfonic acid dissolved in 1 ml. of tetrahydrofuran. After the reaction is finished, in about 0.5 hr., the mixture is washed with 5% aqueous sodium bicarbonat . The organic phase is dried over sodium sulfat and concentrated. The r sidue is subjected to silica gel chromatography, eluting with ethyl ac tat -Skellysolve B (60:40) to yield th formula-XXXIV compound.

f. 3α-Tetrahydropyran-2-yl xy-5α-hydroxy-2β-(3-hydroxy-trans-1-propenyl)-1α-cyclop ntan acetic acid, γ-lactone (Formula-XXXV). The formula-XXXIV propionate, (step e, 3.0 g.) in 10 ml. f m thanol is added to soluti n of sodium methoxide (freshly prepared from 20 mg. of sodium

in 40 ml. of anhydrous m than l). After the r action is compl te, in about 20 min., the m thanol is rem ved und r reduced pressure. The residue is partitioned between dichloromethane and 0.4 M phosphate buffer of pH 4.5. The organic phase is dried over sodium sulfate and c ncentrated to yield the formula-XXXV compound.

g. 3α-Tetrahydropyran-2-yloxy-5α-hydroxy-2β-(trans-2-formylethenyl)-1α-cyclopentaneacetic acid, γ-lactone (Formula XXXVI). An oxidizing reag nt is prepared from chromium trioxide (5.4 g.) and 3,5-dimethylpyrazole (5.2 g.) in 150 ml. of dichloromethane, stirred for 15 min. To the solution is then added the formula-XXXV 3-hydroxy compound (step f, 1.8 g.) dissolved in 20 ml. of dichloromethane. After the reaction is finished, in about 5 min., the mixture is washed with 5% aqueous bicarbonate. The organic phase is dried over sodium sulfate and concentrated. The residue is subjected to silica gel chromatography, eluting with acetone-dichloromethane (1:9) to yield the formula-XXXVI compound.

EXAMPLE 1 3α, 5α-Dihydroxy-2β-[(3R,S)-3-hydroxy-trans-1,7-octadienyl]-1α-cyclopentane-acetic Acid γ-Lactone, 3-tetrahydropyran-2-yl ether and also 3,3'-bis-(tetrahydropyran-2-yl ether) (Formula XXVIII)

I. Via Lactone XXVI. Refer to Chart 2.

A. A solution of lactone XXXVI, i.e. 5α-hydroxy-3α-tetrahydropyran-2-yloxy-2β-(trans-2-formylethenyl)-1α-cyclopentaneacetic acid, γ-lactone (2.775 g., Preparation 1) in 40 ml. of diethyl ether and 10 ml. of tetrahydrofuran is treated at −70°C. with 1-pentenylmagnesium bromide (prepared from 5-bromo-1-pentene (4.115 g.) and magnesium (0.667 g.) in 40 ml. of diethyl ether) added dropwise over 17 min. The mixture is then stirred at about −60°C. for 22 min. and quenched with saturated aqueous ammonium chloride. Sodium sulfate powder is added for coagulation and the solids filtered off. The filtrate, together with ether washings, is dried and concentrated to an oil, 3.109 g. The product is chromatographed, eluting with methylene chloride-acetone (6:1) to obtain the mono-THP ether, mixed C—15 epimers, 2.427 g., having R_f 0.34 and 0.29 (in methylene chloride-acetone (4:1)), NMR peaks at 6.20—5.4, 5.2—4.78, 4.68, 4.3—3.2, 3.02—2.4, 2.35—1.85, and 1.8—1.2 δ, infrared absorption at 3450, 2995, 1775, 1200, 1180, 1120, 1075, 1030, 1020, 975, 920, 870, and 815 cm^{-1}, and mass spectral lines at 422.2446, 407, 353, 337, 321, 320, 269, 251, and 85.

b. The above mono-THP ether is treated in methylene chloride solution with excess dihydropyran in the presence of pyridine hydrochloride at about 25°C. for 16 hr. The mixture is diluted with about 300 ml. of methylene chloride and washed with 5% aqueous sodium bicarboante, water, and brine, and dried. Concentration yields the formula-XXXVIII bis-THP ether title compound, viz. 3α, 5α-dihydroxy-2β-[(3R,S)-3-hydroxy- trans-1,7-octadienyl]-1α-cyclopentaneacetic acid γ-lactone, 3,3'-bis(tetrahydropyran-2-yl ether).

II. Via Lactone XXXVII. Refer to Chart 3. A phosphonate reagent is first prepared. Methyl 5-hexanoate is prepared from 5-hexenoic acid by reaction with methanol and concentrated sulfuric acid in refluxing ethylene dichloride, thereafter washing and distilling the product. The anion of dimethyl methylphosphonate, prepared from dimethyl methylphosphonate (82 g.) and 400 ml. of 1.6 M butyllithium in 800 ml. of tetrahydrofuran at −55 to −60° C. is treated with methyl 5-hexenoate (41 g.) added in 65 ml. of tetrahydrofuran over about 10 min. The mixture is stirred at −75°C. for 2 hr. and then at about 25°C. for 18 hr. Acetic acid (26 ml.) is added and the solvent removed under reduced pressure. The residue is taken up in water and ether-methylene chloride (3:1). The organic phase, combined with extractions of the aqueous phase, is washed with cold aqueous sodium bicarbonate and brine, dried, and concentrated. There is obtained on distillation, dimethyl 2-oxo-heptenylphosphonate.

a. The formula-XXXVI bicylic aldehyde wherein R is benzoyl, i.e. 2-hydroxy-4-benzoxy-5-carboxaldehyde-cyclopentanyl acetic acid γ-lactone (U.S. Patent 3,778,450, 14.5 g.) is added in methylene chloride solution (100 ml.) to the ylid prepared from 25.5 g. of the above phosphonate and 4.2 g. of sodium hydride (57% dispersion) in tetrahydrofuran (500 ml.) first at 0° and then at 20°C. The reaction mixture is warmed from 0° to about 25°C. for one hr., then acidified with 10 ml. of acetic acid and concentrated. The residue is diluted with water and extracted with ether-methylene chloride (3:1). The extracts are washed with cold dilute hydrochloric acid, water, cold aqueous sodium bicarbonate and brine, dried, and concentrated. The residue is chromatographed to yield the formula-XXXVIII 3-oxo-trans-1,7-octadienyl lactone with benzoate blocking group.

b. The formula-XXXIX 3-hydroxy compound, i.e. 5-hydroxy-3-benzoxy-2β-[(3R,S)-3-hydroxy-trans-1,7-octadienyl]-1α-cyclopentaneacetic acid γ-lactone is obtained on reduction with zinc borohydride. For this purpose sodium borohydride (3.78 g.) and anhydrous zinc chloride (13.7 g.) are reacted in 1,2-dimethoxyethane at 0—25°C. The solution of the reagent is cooled to −20°C. and treated dropwise under nitrogen with a solution of the above 3-ox compound (10.0 g.) in 75 ml. of dimethoxyethane. When the reaction is complet d as sh wn by TLC, xcess borohydride is destroyed by careful addition of water and stirring. The mixture is filter d and the filtrat washed with water and brin , dri d, and c ncentrated. The residue is chromatograph d.

c. The benzoat group is r moved by treatment of th above product of step b (3.55 g.) with potassium carbonate (1.23 g.) in methan l at about 25°C. for 1.25 hr. The solvent is rem ved under reduc d pr ssur and th residue is acidified with cold aqu ous potassium hydrogen sulfate and

extracted with thyl acetat . The organic phase is washed with water and brine, dried, and concentrated. Th residue is lactonized in refluxing benzen for 18 hr. and is thereaft r chromatographed to yield the unblocked alkadi nyl lactone, i.e. 3α,5α-dihydroxy-2β-[(3R,S)-3-hydroxy-trans-1,7-octadienyl]-1α-cyclop ntaneacetic acid γ-lact ne.

The abov unblocked lact ne is treated with excess dihydropyran in the presence of pyridine hydrochloride and worked up as in I-b above to obtain the formula-XXVIII bis-THP ether title compound.

EXAMPLE 2 3α,5α-Dihydroxy-2β-[(3S)-3-hydroxy-trans-1,7-octadientyl]-1α-cyclopentaneacetic Acid γ-Lactol, 3,3'-bis-(tetrahydropyran-2-yl Ether) (Formula LIII)

I. Refer to Chart 7. There is first prepared the (3S)-mono-THP 1,7-octadienyl lactone following the procedures of Chart 2 and Example 1—I. A Grignard reagent is prepared in 170 ml. of ether from magnesium (3.14 g.) and 5-bromo-1-pentene (20.80 g.) added dropwise. The reaction mixture is r fluxed for one hr., then cooled and added to a solution of the formula-XXVI aldehyde, i.e. 5α-hydroxy-3α-tetrahydropyran-2-yloxy-2β-(trans-2-formylethenyl)-1α-cyclopentaneacetic acid, γ-lactone (24.43 g., Preparation 1) in 250 ml. of diethyl ether at −70°C. over a period of 22 min. The mixture is stirred for an additional 45 min. at −70°, then poured into a mixture of saturated ammonium chloride solution (900 ml.)-ice-ether (300 ml.). The organic phase is separated, combined with extracts of the aqueous layer, dried, and concentrated. The residue is chromatographed, eluting with acetone-methylene chloride (1:8) to (1:6) to yield the mixed 3(S) and 3(R) mono-THP lactones. They are separated by high pressure liquid chromatography on a series of Merck "B" prepacked columns, eluting with acetone-methylene chloride (1:10), to yield the mono-THP 3(S) isomer, 7.92 g. having R_f 0.34 (in acetone-methylene chloride (1:4)), and the same spectral properties reported in Example 1—I—a. There is also obtained the mono-THP 3(R) isomer, 8.83 g., having R_f 0.29 and substantially the same spectral properties.

Continuing with the above 3(S) compound, namely 3α,5α-dihydroxy-2β-[(3S)-3-hydroxy-trans-1,7-octadienyl]-1α-cyclopentaneacetic acid γ-lactone, 3-(tetrahydropyran-2-yl ether), there is next prepared the formula-VIII bis(THP ether) intermediate. The above 3(S) compound (7.92 g.) is treated in 55 ml. of methylene chloride with pyridine hydrochloride (about 0.7 g.) and dihydropyran (3.42 g.) at about 25°C. After 2 hr. the mixture is warmed and stirred at 32—35°C. for 4 hr. The mixture is cooled in an ice bath, diluted with 100 ml. of methylene chloride, washed with cold 5% sodium bicarbonate and brine, dried, and concentrated to the bis(THP ether) intermediate, 9.88 g. having R_f 0.70 (in acetone-methylene chloride (1:6)).

II. The lactone of part I (9.82 g.) is treated in 100 ml. of toluene at −68°C. with diisobutylaluminum hydride (22.65 ml. of 1.5 M. toluene solution) added dropwise over 8 min. The mixture is stirred at −75° for one hr. and then 10 ml. of saturated aqueous sodium sulfate added. The mixture is warmed to room temperature, diluted with 700 ml. of diethyl ether, and treated with powdered sodium sulfate. The solids are removed on a Celite filter. The filtrate is dried and concentrated to yield the formula-LIII lactol title compound, having R_f 0.35 (in acetone-methylene chloride (1:6)).

EXAMPLE 3 19,20-Didehydro-PGF$_2\alpha$, 11,15-bis-(tetrahydropyran-2-yl Ether) (Formula LIV) and Methyl Ester

Refer to Chart 7. The lactol of Example 2 (9.87 g.) is alkylated by the Wittig reaction. The Wittig r agent is first prepared from 4-carboxybutyl triphenylphosphonium bromide (35.1 g.) added to the reaction product of sodium hydride (7.6 g.) and 180 ml. of dimethyl sulfoxide previously warmed to 70—75°C. for 1.5 hr. and then cooled to about 25°C. for 25 min. then treated with the formula-LIII (3S) lactol in 65 ml. of dimethylsulfoxide added dropwise over 25 min. and stirred additional 30 min. The mixture is acidified in ice water with 2 N potassium hydrogen sulfate and then extracted with ether. The organic phase is washed with brine, dried, and concentrated to yield the formula-LIV bis-THP free acid.

The acid is then esterified with ethereal diazomethane and the resulting methyl ester is chromatographed to yield the title methyl ester 9.37 g., having R_f 0.62 (in acetone-methylene chloride (1:6)), and NMR peaks at 6.18—4.56, 4.37—3.20, 3.65, and 2.78—1.11 δ.

EXAMPLE 4 19,20-Didehydro-PGF$_2\alpha$ and 19,20-Didehydro-PGF$_2\alpha$, Methyl Ester (Formula LV).

Refer to Chart 7.

The bis-THP ether of the title acid (Example 3) is hydrolyzed to acetic acid: water: tetrahydrofuran (20:10:3) at 40°C. for 3 hr. The solvents are removed under reduced pressure and the residue is chromatographed on silica gel, eluting with ethyl acetate-hexane (1:1) t yield the title acid.

The bis-THP ether of the titl methyl est r (Example 3) is likewise hydrolyzed in acetic acid:water:tetrahydrofuran(20:10:3) f llowing the same procedure to yield th title compound having R_f 0.48 (in ethyl acetat -m thanol (10:1)), and mass spectral lines at 582.3570, 567, 551, 541, 513, 492, 423, 402, and 217.

EXAMPLE 5 19,20-Didehydr -(15R)-PGF$_2\alpha$, Methyl Ester (Formula LV).

Ref r to Chart 7. Foll wing the procedures f Examples 2—4, but utilizing the (3R) isomer of

Example 2—I, namely 3α, 5α-dihydroxy-2β-[(3R)-3-hydroxy-trans-1,7-octadi nyl]-1α-cyclopentaneacetic acid γ-lactone, 3(tetrahydropyran-2-yl eth r) there is prepared the corresponding formula-VIII (3R) bis(THP ther) intermediate and the formula-LIII lactol, then by Wittig alkylation the formula-LIV 19,20-didehydro-(15R)-PGF$_2\alpha$, 11,15-bis-(tetrahydr pyran-2-yl ether). Finally, after sterificati n and hydrolysis of the blocking groups, the title compound is obtained, having R_f 0.66 (TLC on silica gel in ethyl acetat -methanol (10:1)).

EXAMPLE 6 19,20-Didehydro-PGF$_2\alpha$, Methyl Ester (Formula LV) and 19,20-Didehydro-15R-PGF$_2\alpha$, Methyl Ester (Formula LV).

Following the procedure of Example 2—II, the (3R,S) mono-THP lactone of Example 2—I (1.720 g.) is reduced to the corresponding lactol, using 26.3 ml. of 0.56 M diisobutylaluminum hydride at about −75°C. There is obtained 1.660 g. of lactol, having R_f 0.17 (in methylene chloride-acetone (4:1)), and infrared absorption at 3450, 2995, 1130, 1200, 1070, 1020, 975, 915, 870, and 815 cm^{-1}.

Following the procedure of Example 3, the above lactol (1.620 g.) is alkylated by the Wittig reaction using the ylid prepared from 4-carboxybutyl triphenylphosphonium bromide (9.105 g.) to yield the corresponding acid. The acid is esterified in methanol-ether with ethereal diazomethane to yield 3.497 g. The ester is chromatographed, eluting with ethyl acetate-Skellysolve B (1:1), to yield the mono-THP mixed C—15 epimers, 1.536 g., having R_f 0.47 and 0.38 (in ethyl acetate-Skellysolve B (1:1)) and infrared absorption at 3450, 2990, 1740, 1430, 1200, 1020, 975, 910, 870 and 815 cm^{-1}.

The above mono-THP product is hydrolyzed in acetic acid-water-tetrahydrofuran (20:10:3) at 40°C. for 3 hr., thereafter concentrating. The resulting oil is chromatographed, eluting with ethyl acetate-Skellysolve B (16—0%) to yield first the (15R) title compound, 0.070 g., then a mixture, and finally the (15S) title compound, 0.083 g. The (15R) compound has R_f 0.66, the (15S) has R_f 0.48 (in ethyl acetate-methanol (10:1)), and both have mass spectral peaks at 582.3570, 567, 551, 541, 513, 492, 423, 402, and 217.

EXAMPLE 7 19,20-Didehydro-PGE$_2$, Methyl Ester (Formula III).

Refer to Chart 1. The formula-IX 11,15-bis(tetrahydropyran-2-yl ether), available from Example 3, is oxidized by the Jones reagent. Thereafter the THP blocking groups are replaced by hydrogen to yield the title compound.

EXAMPLE 8 19,20-Didehydro-PGF$_2\alpha$, p-Acetylphenyl Ester

The mixed anhydride is first prepared. A solution of 19,20-didehydro-PGF$_2\alpha$ (Example 4) in methylene chloride is treated with triethylamine (2 equiv.) and isobutylchloroformate (1.01 equiv.) at about 25°C. for 0.5 hr. Solid p-hydroxyacetophenone (1.01 equiv.) is added and stirring continued for 4 hr. The mixture is diluted with methylene chloride, washed with water, 0.1 N sodium hydroxide, water, and brine, dried, and concentrated. The product is chromatographed on silica gel eluting with acetone-hexane to yield the title compound.

EXAMPLE 9 19,20-Didehydro-PGF$_2\alpha$, Sodium Salt

A solution of 19,20-didehydro-PGF$_2\alpha$, (Example 3) in methanol is neutralized with a solution of sodium carbonate in water. The mixture is concentrated to a small volume, diluted with acetonitrile and concentrated to a residue of the title compound.

EXAMPLE 10 19,20-Didehydro-PGF$_2\alpha$, Amide

Refer to Chart 17. The formula-CIX mixed anhydride is prepared following the procedure of Example 8. There is then added at about −5°C., a saturated solution of ammonia in acetonitrile and the mixture stirred at −5°C. for 10 min. The reaction mixture is diluted with brine and water (5:1) and extracted with ether. The organic phase is washed with brine and 2 N hydrochloric acid, then with brine and 5% sodium bicarbonate, finally with brine, dried and concentrated. The residue is chromatographed on a HPLC silica gel column, eluting with acetone to yield the title compound.

EXAMPLE 11 19,20-Didehydro-PGF$_2\alpha$, Methanesulfonamide (Formula CXV)

Refer to Chart 18. A solution of mixed anhydride in dimethylformamide (prepared from 19,20-didehydro-PGF$_2$ of Example 4 by reaction with isobutylchloroformate in the presence of triethylamine as in Example 8) is treated, with stirring, at 0°C. with about 4 equivalents of methanesulfonamide sodium salt (prepared from methanesulfonamide and methanolic sodium methoxide in methanol, concentrating and azeotroping with benzene), thereaft r adding sufficient hexamethylphosphoramide to insure a homogenous mixture. The mixture is stirred at about 25°C. for 18 hr., then acidified with cold dilute hydrochloric acid and extracted with ethyl acetate. The organic phase is washed with water and brine, dried, and c ncentrated. The residu is chromat graphed on silica gel, eluting with methanol-methylene chloride, to yield the title compound.

EXAMPLE 12 3α, 5α-Dihydroxy-2β-(3-oxo-trans-1,7-octadienyl)-1α-cyclopentaneacetic Acid γ-Lactone, 3-tetrahydropyran-2-yl Ether (Formula CXXIII)

Refer to Chart 21. The formula-XXXVIII 3-oxo intermediate of Example 1—II—a is deblocked by treatment with potassium carbonate in methanol at about 25°C. for 1.25 hr., following the procedure of Example 1—II—c. Thereafter, the THP ether is formed with excess dihydropyran in the presence of pyridine hydrochloride to yield the title compound.

Alternatively, the 3-hydroxy mono-THP lactones of Example 2 are oxidized by Jones reagent. Thus, the mono-THP 1,7-octadienyl lactone (8.83 g.) is treated in acetone at −35°C with Jones Reagent (17 ml. of 2.67 M) added dropwise. Then stirring is continued for 35 min. and finally isopropanol (6.0 ml.) added with additional stirring. The mixture is added to a mixture of 5% sodium bicarbonate and ice-water and extracted with ether. The organic phase is washed with brine, dried, and concentrated to yield the title compound, 7.63 g., having R_f 0.52 (in ethyl acetate-Skellysolve B (2:1)).

EXAMPLE 13 3α,5α-Dihydroxy-2β-[(3R,S)-3-hydroxy-3-methyl-trans-1,7-octadientyl]-1α-cyclopentaneacetic Acid γ-Lactone, 3-tetrahydropyran-2-yl ether (Formula CXXIV).

Refer to Chart 21. The formula-CXXIII 3-oxo lactone (Example 12, 7.63 g.) in 500 ml. of tetrahydrofuran is treated at −78°C. with methylmagnesium bromide (35.4 ml. of 3.1 M) added dropwise over 20 min. Stirring is continued for 2.5 hr. at about −60°C. and then the reaction is quenched with 400 ml. of saturated aqueous ammonium chloride and 300 ml. of ice water and ether is added. The organic phase is separated, combined with organic extracts of the aqueous phase, dried, and concentrated. The residue is chromatographed, eluting with ethyl acetate-Skellysolve B (2:1) to yield the mono (THP ether) of the title compound having R_f 0.27 (in ethyl acetate-Skellysolve B (2:1)), NMR peaks at 6.20—5.40, 5.40—4.52, 4.30—3.18, 3.07—1.35, and 1.23 δ; and infrared absorption at 3400, 2850, 1740, 1620, 1420, 1330, 1150, 1110, 1060, 1020, 965, 900, 960, and 805 cm^{-1}.

EXAMPLE 14 3α,5α-Dihydroxy-2β-[(3R,S)-3-hydroxy-3-methyl-trans-1,7-octadienyl]-1α-cyclopentaneacetic Acid γ-Lactol, 3-tetrahydropyran-2-yl Ether (Formula CXXV)

Refer to Chart 21. The formula-CXXIV lactone (Example 13, 5.20 g.) in 100 ml. of toluene at −68°C. is treated with diisobutylaluminum hydride (23.8 ml. of 1.5 M. toluene solution) added dropwise over 8 min. Thereafter following the procedure of Example 2—II, there is obtained the formula-CXXV lactol title compound, 3.79 g., having R_f 0.31 (in acetone-methylene chloride (1:3)), NMR peaks at 6.18—5.37, 5.33—4.29, 4.25—3.21, 3.05—1.34, and 1.26 δ, and IR absorption at 3350, 2900, 1640, 1440, 1340, 1260, 1200, 1120, 1060, 970, 910, 865, and 810 cm^{-1}.

EXAMPLE 15 (15R,S)-15-Methyl-19,20-didehydro-$PGF_2\alpha$, 11-tetrahydropyran-2-yl Ether, Methyl ester (Formula CXXVI).

Refer to Chart 21. The formula-CXXV lactol (Example 14, 3.79 g.) is subjected to the Wittig reaction following the procedure of Example 3, and thereafter esterified to yield the formula-CXXVI title compound, having R_f 0.34 (in acetone-methylene chloride (1:6)), NMR peaks at 6.16—5.20, 5.20—4.55, 4.27—3.17, 3.65, 2.67—1.34, and 1.27 δ, and infrared absorption at 3400, 2900, 1720, 1630, 1430, 1340, 1190, 1120, 1085, 1010, 965, 900, 860, and 805 cm^{-1}

EXAMPLE 16 15-Methyl-19,20-didehydro-$PGF_2\alpha$, Methyl Ester (Formula LV) and (15R)-15-Methyl-19,20-didehydro-$PGF_2\alpha$, Methyl Ester (Formula LV).

Refer to Chart 21. The product of Example 15 is hydrolyzed to replace tetrahydropyranyl groups in the usual way, for which see Example 4. The 15-epimers are separated by silica gel chromatography to yield the title compounds.

EXAMPLE 17 3α,5α-Dihydroxy-2β-[(3R,S) (7R,S)-3,7-dihydroxy-trans-1-octenyl]-1α-cyclopentaneacetic Acid γ-Lactone, 3,3′-bis(Tetrahydropyran-2-yl Ether) (Formula CXXIX)

Refer to Chart 23. The title compound is obtained by oxymercuration-demurcuration. The formula-VIII alkadienyl lactone, i.e. 3α,5α-dihydroxy-2β-[(3R,S)-3-hydroxy-trans-1,7-octadienyl]-1α-cyclopentaneacetic acid γ-lactone, 3,3′-bis(tetrahydropyran-2-yl ether) (Example 1, 14.54 g.) is added dropwise to a stirred suspension of mercuric acetate (14.946 g.) in 120 ml. of water and 120 ml. of tetrahydrofuran and the mixture is stirred at about 25°C. for 22 hr. The mixture is cooled in an ice bath and treated with sodium borohydride (3.752 g.) added in portions over 6—8 min. The temperature is raised to about 25°C. and stirring continued for 3 min. The mixture is diluted with ether (300 ml.) decanted from mercury, separated, and the organic phase combined with ether extracts of the aqueous phase. The organic phase is washed with brine, dried, and concentrated to an oil, 15.88 g. The oil is chromatographed on silica gel, eluting with acetone-methylene chloride (1:4 to 2:4) to obtain the formula CXXIX 7-hydroxy title compound, 11.568 g., having R_f 0.38 (TLC on silica gel in acetone-methylene chloride (1:3)), NMR peaks at 5.50, 5.00, 4.63, 4.20—3.10, 3.00—1.20, and 1.15 δ, and infrared absorption at 3500, 2990, 1775, 1120, 1020, 970, 910, 865, 810, and 730 cm^{-1}

EXAMPLE 18 2-Decarboxy-2-hydroxymethyl-(19R,S)-19-hydroxy-PGE_1 (Formula CXLIV) and 2-Decarboxy-2-hydroxymethyl-13,14-dihydro-(19R,S)-19-hydroxy-PGE_1 (Formula CXLV).

I. Refer to Chart 24. Th formula-CXXXV compound is first prepared. The formula-CXXXIV compound, nam ly 19,20-didehydro-$PGF_2\alpha$, 11,15-bis(tetrahydropyran-2-yl th r), methyl ester (Example 3, 2.60 g.) is silylated with dimethyl-t-butyl-chlorosilane (1.465 g.) in 10 ml. of dimethylformamide and 1.325 g. of imidazole for 16 hr. at about 25°C. The mixture is diluted with ice-water and extracted with diethyl ether. The extracts are washed, dried, concentrated, and chromatographed to yield the formula-CXXXV 19,20-didehydro-9(dimethyl-t-butylsilyl)-$PGF_2\alpha$, 11,15-bis(tetrahydropyran-2-yl ether), methyl ester having R_f 0.69 (in ethyl acetate-Skellysolve B (1:4)).

II. The formula-CXXXVI compound is prepared by oxymercuration-demercuration. The formula-CXXXVI compound (11.30 g.) in 100 ml. of tetrahydrofuran is added dropwise over a 15 minute period to a stirred suspension of mercuric acetate (7.76 g.) in 100 ml. of water and 100 ml. of tetrahydrofuran at about 25°C. After 3.75 hr. the mixture is cooled to 5°C. and treated with sodium borohydride (1.46 g.). The mixture is stirred an additional 5 min. without cooling, then diluted with ether and filtered. The organic phase, together with ether-extracts of the aqueous phase, is dried and concentrated. The residue is chromatographed, eluting with ethyl acetate-Skellysolve B (1:2 to 1:1) to yield the formula-CXXXVI compound, 9-(dimethyl-t-butylsilyl)-(19R,S)-19-hydroxy-$PGF_2\alpha$, 11,15-bis(tetrahydropyran-2-yl ether), methyl ester, 8.86 g., having R_f 0.23 (TLC on silica gel in ethyl acetate-Skellysolve B (1:2)), and NMR peaks at 5.72—5.15, 4.76—4.46, 4.28—3.09, 3.58, 2.74—1.22, 1.08, and 0.87 δ.

III. The above material is reduced with hydrogen over palladium (5%)-on-carbon catalyst (0.250 g.) in 75 ml. of ethyl acetate containing about 0.3 ml. of acetic acid. Additional catalyst and acetic acid are added as necessary to obtain 106 ml. uptake of hydrogen. The product (CXXXVII) is a mixture of the PGE_1 and 13,14-dihydro compounds in a ratio of about 0.4/0.6.

IV. The above formula-CXXXVII compounds (about 2.55 g.) are treated with dihydropyran (1.50 mT.) and pyridine hydrochloride (0.120 g.) in 40 ml. of methylene chloride for 15 hr. at about 25°C. The mixture is diluted with 175 ml. of methylene chloride, washed with 5% aqueous sodium bicarbonate, water, and brine, dried and concentrated to the formula-CXXXVIII compounds, 2.765 g.

V. The above methyl esters are reduced with lithium aluminum hydride (0.278 g.) in 10 ml. of diethyl ether with stirring for 1.5 hr. at about 25°C. The mixture is chilled and quenched with saturated aqueous sodium sulfate, diluted with ether, and treated with powdered sodium sulfate. The mixture is filtered, washed with ether, concentrated and dried to an oil, 2.542 g. represented by formula CXXXIX.

VI. The formula-CXXXIX C—1 alcohols are blocked by treating with dihydropyran (1.40 ml.) and pyridine hydrochloride (0.120 g.) in 40 ml. of methylene dichloride for about 17 hr. at about 25°C. After the usual work-up there is obtained 2.829 g. of an oil represented by formula-CXL.

VII. The above product is desilylated in preparation for oxidation at C—9. The product of VI is treated with n-tetrabutylammonium fluoride (12 ml. of 0.75 M in tetrahydrofuran with 15 ml. of tetrahydrofuran) for about 6.5 hr. at 25°C. and one hr. at 40°C. There is added an additional 3 ml. of reagent and the reaction continued at 40°C. for one hr. The mixture is diluted with 250 ml. of ether, washed with brine, water, and brine, dried and concentrated. The mixture is chromatographed to yield an oil, 1.970 g., represented by formula CXLI.

VIII. The formula-CXLI product of VII above is oxidized with Jones reagent, using 1.85 ml. (2.67 M) in 65 ml. of acetone, quenching with 3 ml. of isopropanol, to yield 1.910 g. of the mixed formula-CXLIII compounds.

IX. The product of VIII is hydrolyzed to remove blocking groups, using 80 ml. of acetic acid-water-tetrahydrofuran (20:10:3) for 4 hr. at about 45°C. The solvents are removed azeotropically with benzene to give an oil, 1.680 g. The residue is chromatographed by HPLC, eluting with acetone-methylene chloride (2:1), to yield (after some mechanical losses) the PGE_1-type title compound (0.114 g.) and the less polar 13,14-dihydro-PGE_1-type title compound (0.230 g.), CXLIV and CXLV respectively.

EXAMPLE 19 2-Decarboxy-2-hydroxymethyl-(19R,S)-19-hydroxy-$PGF_1\alpha$ and 2-Decarboxy-2-hydroxymethyl-13,14-dihydro-(19R,S)-19-hydroxy-$PGF_1\alpha$

Refer to Chart 24. The formula-CXLI compounds are deblocked in dilute acid to yield CXLII, the mixed title compounds, which are separated by silica gel chromatography.

EXAMPLE 20 2-Decarboxy-2-hydroxymethyl-(19R,S)-19-hydroxy-$PGF_{1\alpha}$ (Formula CL)

I. Refer t Chart 25. The formula-CXLVI starting material, namely 19,20-didehydro-$PGF_2\alpha$, 11,15-bis-(t tra-hydropyran-2-yl ether), methyl ester (Example 3), is first oxymercurated. A stirred suspension of mercuric acetate (7.76 g.) in 100 ml. of water and 100 ml. of tetrahydrofuran is treated with 19,20-didehydro-$PGF_2\alpha$, methyl ester (9.25 g.) in 100 ml. f tetrahydrofuran added dropwise at 25°C. in about 15 min. The mixture is stirred at about 25°C. for 3.75 hr., cooled to 5°C. and treated with portions of sodium borohydride (1.46 g.) demercurat . Stirring is continued for 5 min. while warming to about

25°C. Th mixture is diluted with eth r (about one 1.) and filtered through Celite. Th organic phase is dried and conc ntrated to crude CXLVII. The residue is chr matographed, eluting with thyl acetate, to yi ld CXLVII, namely (19R,S)-19-hydroxy-PGF$_2\alpha$, 11,15-bis(tetrahydropyran-2-yl eth r), methyl ester, having R_f 0.38 (in ethyl acetate-Skellysolve B (4:1)), and NMR peaks at 5.89—5.03, 4.83—4.52, 4.28—3.17, 3.65, 2.78—1.28, and 1.18 δ.

II. Next is prepared the formula-CXLVIII corresponding PGF$_1\alpha$ compound. Compound CXLVII above (1.270 g.) in 40 ml. of ethyl acetate together with 0.130 g. of 5 percent palladium-on-carbon catalyst is reduced with hydrogen at one atmosphere at about 25°C. The catalyst is filtered off and the filtrate is concentrated to yield the formula-CXLVIII compound, namely (19R,S)-19-hydroxy-PGF$_1\alpha$, 11,15-bis(tetrahydropyran-2-yl ether), methyl ester, 1.230 g., having NMR peaks at 5.50, 4.70, 4.30—3.20, 3.67, 2.50, 2.70—1.20, and 1.15 δ, and infrared absorption at 3500, 2995, 1730, 1430, 1200, 1020, 970, 865, and 805 cm^{-1}.

III. The corresponding C-1 alcohol is obtained by reduction. A solution of compound CXLVIII above (1.230 g.) in 15 ml. of ether is added to an ice-cold suspension of lithium aluminum hydride (0.337 g.) in 10 ml. of ether. An additional 20 ml. of ether is added and the mixture is stirred at about 25°C. for one hr. Thereafter about 7 ml. of saturated aqueous sodium sulfate is added dropwise, and solid sodium sulfate to coagulate aluminum salts, and the mixture is filtered. The filtrate is concentrated to an oil, 1.150 g. The procedure of reduction is repeated if necessary to convert unreacted formula-CXLVIII material. The resulting oil is chromatographed by HPLC on a Merck "B" column, eluting with ethyl acetate-Skellysolve B (9:1)), to yield the formula-CXLIX compound, namely 2-decarboxy-2-hydroxymethyl-(19R,S)-19-hydroxy-PGF$_1\alpha$, 11,15-bis(tetrahydropyran-2-yl ether), 0.985 g., having NMR peaks at 5.50, 4.70, 4.25—3.20, 2.80, 2.60—1.20, and 1.15 δ, and infrared absorption at 3400, 2990, 1430, 1120, 1020, 970, 900, 860, and 805 cm^{-1}.

IV. The formula-CL title compound is obtained on deblocking the formula-CXLIX compound above in acetic acid-water-tetrahydrofuran (20:10:3) at about 40—45°C for 45 min., concentrating, and chromatographing.

EXAMPLE 21 9-(Dimethyl-t-butylsilyl)-19-keto-PGF$_2\alpha$, bis(Tetrahydropyranyl Ether) (Formula CLXIX) and 19-Keto-PGF$_2\alpha$, Methyl Ester (Formula CLXX)

I. Refer to Chart 29. The formula-CXXXVI product of Example 18 (0.500 g.) in 8 ml. of methylene chloride is added to Collins reagent (prepared from chromic anhydride (0.526 g.) in pyridine (0.831 g.)) and methylene chloride at 0°C. The mixture is stirred at about 25°C. for 1.2 hr., then diluted with 200 ml. of ether, filtered, and concentrated. The residue (0.502 g.) consists of the formula-CLXIX 9-silyl-11,15-bis(THP ether)-19-keto compound.

II. The product of I is hydrolyzed in tetrahydrofuran-acetic acid-water (3:20:10) at 47—50°C. for 4 hr. The mixture is concentrated and then chromatographed eluting with acetone-methylene chloride (1:1). There is obtained the title compound, 0.128 g., having R_f 0.33 (TLC on silica gel in acetone-methylene chloride (1:1)), NMR peaks at 5.87—5.06, 4.60—3.12, 3.65, 2.69—0.84, and 2.13 δ; infrared absorption at 3350, 2900, 1730, 1430, 1350, 1220, 1160, and 965 cm^{-1}, and mass spectral lines at 598.3545, 583, 513, 508, 493, 423, 418, 217, and 187.

EXAMPLE 22 (15R)-19-Keto-PGF$_2\alpha$ (Formula CLXX)

Refer to Charts 24 and 29. Following the procedures of Examples 3, 18, and 21 but replacing the (3S) lactone isomer of Example 3 with the corresponding (3R) isomer obtained in Example 2, there is obtained the title compound, having R_f 0.27 (TLC on silica gel in methylene chloride-acetone (1:1)), NMR peaks at 5.70—5.15, 4.10, 3.67, 3.20, 2.17, and 2.70—1.20 δ; infrared absorption at 3300, 2990, 1710, 1420, 1350, and 965 cm^{-1}; and high resolution mass spectral line at 598.3516.

EXAMPLE 23 19-Keto-13,14-dihydro-PGF$_1\alpha$, Methyl Ester (Formula III)

I. The formula-CXXXVI product of Example 18—II, i.e. 9-dimethyl-t-butylsilyl-(19R,S)-19-hydroxy-PGF$_{2\alpha}$, 11,15-bis(tetrahydropyran-2-yl ether), methyl ester (2.0 g.) is reduced at C_5—C_6 and C_{13}—C_{14} by catalytic hydrogenation in 75 ml. of ethyl acetate using 200 mg. of 5% palladium-on-carbon catalyst to a mixture of the corresponding PGF$_1\alpha$ and 13,14-dihydro-PGF$_1\alpha$ products which is further hydrogenated to the 13,14-dihydro compound.

II. Following the oxidation procedures of Example 21, the corresponding 9-silyl-11-15-bis(THP ther)-13,14-dihydro-19-keto-PGF$_1\alpha$, methyl ester is obtained.

Ther aft r, by hydrolysis in tetrahydrofuran-acetic acid-water, the title compound is obtained. The TLC and NMR data show the presence of a less polar acetal form as well as the 19-k to form. R_f 0.28, 0.54, and 0.67 (TLC n silica gel in A—IX solvent); NMR peaks at 4.52—3.30, 3.62, 3.38, 3.00—0.87, 2.08, and 1.18 δ; and mass spectral lines at 512.3336, 528, 517, 497, 427, 422, 412, 369, and 217.

EXAMPLE 24 2-Decarboxy-2-hydroxymethyl-19-ket -PGE$_1$ (Formula CLXXXIII).

I. Refer to Chart 31. The formula-CXLIX compound, namely 2-decarboxy-2-hydroxymethyl-(19R,S)-19-hydroxy-PGF$_{1\alpha}$, 11,15-bis(tetrahydropyranyl ether) (Example 20—III, 0.985 g.) is blocked at C—1 with

silyl by tr ating in 6 ml. of ice-cold dimethylformamid with 0.135 g. f dimethyl-t-butylsilyl chloride and 0.122 g. of imidaz le. The mixture is stored at 0—5°C., for 2 hr., th n treated with additional 0.135 g. of dimethyl-t-butylsilyl chloride and 0.122 g. of imidazole. Finally, after 18 hr. at 0—5°C., the mixture is again tr ated with 0.085 g. of silyl reag nt and stored at 0—5°C. for 3 hr. The mixture is quenched with crush d ice (about 10 g.), stirred, diluted with water, and xtracted with ther. Th organic phase is wash d with water, and brine, dried, and concentrated t an oil, 1.125 g. The oil is chromatographed by HPLC, eluting with ethyl acetate-Skellysolve B (1:1), to yield the formula-CLXXXI compound, 0.475 g. having NMR peaks at 5.50, 4.70, 4.30—3.30, 2.70—1.25, 1.15, 0.90, and 0.03 δ, and infrared absorption at 3500, 2995, 1460, 1225, 1100, 1020, 835, and 770 cm^{-1}.

II. The C—9 and C—19 hydroxy groups of the formula-CLXXXI compound of I are oxidized, using Collins reagent following the procedure of Example 21 but using 1.036 g. of chromic anhydride and 1.66 ml. of pyridine in 54 ml. of methylene chloride with 0.475 g. of CLXXXI above. There is obtained the formula-CLXXXII compound, namely 2-decarboxy-2-hydroxymethyl-19-keto-PGE$_1$, 1-dimethyl-t-butylsilyl ether, 11,15-bis(tetrahydropyran-2-yl ether), 0.428 g., having NMR peaks at 5.60, 4.70, 4.30—3.10, 2.10, 2.85—1.10, 0.90 and 0.05 δ, and infrared absorption at 2990, 1730, 1710, 1460, 1340, 1200, 1100, 970, 830, and 770 cm^{-1}.

III. The product of II above is deblocked in 15 ml. of acetic acid-water-tetrahydrofuran (20:10:3) at 40—45°C. for 3 hr. The solvents are removed azeotropically with chloroform under reduced pressure. The residue is chromatographed, eluting with acetone-methylene chloride (1:1) to yield the formula-CLXXXIII title compound, 0.042 g., and its formula-CLXXXIV hemiacetal, 0.052 g. The hemi-acetal is converted to the 19-keto form in acetic acid-water-tetrahydrofuran. The 19-keto compound has NMR peaks at 5.65 4.15, 3.60, 3.00, 2.13, and 2.65—1.20 δ, infrared absorption at 3400, 2990, 1715, 1350, 1220, 1070, and 965 cm^{-1}, and high resolution mass spectral peak at 570.3626.

EXAMPLE 25 (19R,S)-19-Hydroxy-PGF$_2\alpha$, Methyl Ester, 9,19-bis(dimethyl-t-butylsilyl ester), 11,15-bis(tetrahydropyran-2-yl ether) (Formula CLXXXV)

Refer to Chart 32. Following the procedure of Example 18—I the formula CXXXVI 19-hydroxy compound of Example 18—II (4.34 g.) is silylated to yield the title compound, 4.84 g.

EXAMPLE 26 2-Decarboxy-2-hydroxymethyl-(19R,S)-19-hydroxy-PGF$_2\alpha$, 9,19-bis(dimethyl-t-butyl silyl ether), 11,15-bis(tetrahydropyran-2-yl ether) (Formula CLXXXVI)

Refer to Chart 32. The formula-CLXXXV product of Example 25 (4.84 g.) in 35 ml. of ether is added dropwise to a suspension of lithium aluminum hydride (0.943 g.) in 125 ml. of ether at about 25°C. After 4.5 hr. an additional 0.472 g. of lithium aluminum hydride is added and again after another hour. The mixture is heated at reflux for 30 min., then cooled in an ice bath and quenched with gradual addition of 55 ml. of saturated aqueous sodium sulfate. Anhydrous powdered sodium sulfate is added and the mixture filtered. The filtrate is concentrated to yield the title compound, having R_f 0.58 (TLC on silica gel in ethyl acetate-Skellysolve B (1:2)) and NMR peaks at 5.73—5.00, 4.76—4.43, 4.32—3.12, 2.75—1.19, 1.08, 0.87, and 0.84 δ.

EXAMPLE 27 2-Decarboxy-2-hydroxymethyl-(19R,S)-19-hydroxy-PGF$_2\alpha$, 9,19-bis(dimethyl-t-butyl-silyl ether), 1,11,15-tris(tetrahydropyran-2-yl ether) (Formula CLXXXVII).

Refer to Chart 32. The formula-CLXXXVI product of Example 26 (4.67 g.) in 25 ml. of methylene chloride is treated with dihydropyran (0.941 g.) in the presence of a catalytic amount of pyridine hydrochloride at about 25°C. After 5 hr. additional dihydropyran (0.52 g.) is added. Finally the mixture is diluted with 150 ml. of methylene chloride, washed with 5% aqueous sodium bicarbonate and brine, dried, and concentrated to yield the title compound, 5.25 g., having R_f 0.71 (in ethyl acetate-Skellysolve B (1:2)).

EXAMPLE 28 2-Decarboxy-2-hydroxymethyl-(19R,S)-19-hydroxy-PGF$_2\alpha$, 1,11,15-tris(tetrahydropyran-2-yl ether) (Formula CLXXXVIII)

Refer to Chart 32. The formula-CLXXXVII compound of Example 27 (5.19 g.) is desilylated by treatment in tetrahydrofuran with 8 equivalents of tetra(n-butyl)ammonium fluoride at 40°C. The reaction mixture is diluted with 150 ml. of ethyl acetate, washed with brine and water and brine again, dried, and concentrated. The residue is chromatographed, eluting with ethyl acetate-Skellysolve B (2:1) to yield the title compound, 3.10 g., having R_f 0.35 (in ethyl acetate-Skellysolve B (2:1)) and NMR peaks at 5.75—5.12, 4.84—4.50, 4.35—3.15, 2.73—1.05, and 1.16δ.

EXAMPLE 29 2-Decarboxy-2-hydroxymethyl-(19R,S)-19-hydroxy-PGF$_1\alpha$, 1,11,15-tris(tetrahydropyran-2-yl ether) (Formula CLXXXVIII)

Following th procedure of Example 23 the formula-CLXXXVIII product f Example 28 is catalytically hydrogenated to the PGF$_{1\alpha}$ title c mpound, having R_f 0.32 (in ethyl acetate-Skellysolve B (2:1)) and NMR peaks at 5.73—5.27, 4.89—4.45, 4.33—3.15, 2.83—1.00, and 1.18δ.

EXAMPLE 30 2-Decarboxy-2-hydroxymethyl-19-keto-PGE$_1$ (Formula CXCI)

Ref r to Chart 32. Following the procedure of Example 21 the formula-CLXXXVIII product of Example 29 (1.90 g.) is oxidized and then hydrolyzed to th titl compound, 0.360 g. The product is contaminated with a small amount of the corr sponding cis-Δ^5-13,14-dihydro c mpound. Data for th product are: R_f 0.24 (in ac ton -m thylene chloride (1:1)), NMR peaks at 5.80—5.55, 5.55—5.28 (impurity), 4.60—3.22, 3.53, 2.92—0.95, and 2.08 δ, and infrared absorption at 3300, 2850, 2800, 1700, 1420, 1390, 1340, 1300, 1230, 1150, 1065, 1000, 960, and 720 cm^{-1}.

EXAMPLE 31 2-Decarboxy-2-hydroxymethyl-(19R,S)-19-hydroxy-PGF$_{2}\alpha$ (Formula CLXXXIX)

Refer to Chart 32. Following the procedure of Example 21, the formula-CLXXXVIII compound of Example 28 is deblocked by acid hydrolysis in tetrahydrofuran-acetic acid-water (3:20:10) at about 40—45°C. to yield the title compound.

EXAMPLE 32 2-Decarboxy-2-hydroxymethyl-19-keto-PGE$_2$ (Formula CXCI)

Refer to Chart 32. The formula-CLXXXVIII compound of Example 28 (1.2 g.) is oxidized with Jones reagent (3.6 ml. of 2.67 M) added dropwise to the acetone solution at −35°C., thereafter stirring at about −20°C. for 35 min. The reaction is quenched with isopropanol (6.0 ml.) and stirring continued for 5 min. The mixture is poured into 250 ml. of 5% aqueous sodium bicarbonate and 150 ml. of ice water and extracted with ether. The organic phase is washed with brine, dried, and concentrated. The residue is hydrolyzed to remove blocking groups in tetrahydrofuran-acetic acid-water (3:20:10) at 30°C. for 16 hr. and the solution is concentrated. The residue is chromatographed on a high pressure Merck "B" column eluting with acetone-methylene chloride (1:1) containing 1% acetic acid, to yield the title compound, 0.310 g., having R_f 0.30 (in acetone-methylene chloride (1:1)) and NMR peaks at 5.84—5.52, 5.52—5.00, 4.58—3.78, 3.78—3.16, 2.98—0.90, and 2.07 δ.

EXAMPLE 33 3α,5α-Dihydroxy-2β-[(3RS)-3-hydroxy-7-oxo-trans-1-octenyl)-1α-cyclopentaneacetic Acid γ-Lactone, 3,3'-bis(Tetrahydropyran-2-yl Ether) (Formula CXCVII).

Refer to Chart 34. The formula-CXXIX 7-hydroxy lactone (Example 17, 10.02 g.) in 300 ml. of acetone is treated at −30°C. with Jones reagent (14.95 ml. of 2.67 M) added dropwise within 10 min. The mixture is stirred at −25 to −20°C. for additional 18 min., then quenched with 20 ml. of isopropanol and stirred 5 min. more. The mixture is added to 500 ml. of cold 5% sodium bicarbonate and 800 ml. of ethyl acetate, separated, and the organic phase is combined with ether extracts of the aqueous phase. The organic phase is washed with 5% sodium bicarbonate, ice water, and brine, dried and concentrated to yield the title compound, 9.93 g., having R_f 0.64 (TLC on silica gel in acetone-methylene chloride (1:3), and NMR peaks at 5.50, 5.00, 4.63, 4.25—3.0), 2.13, and 3.00—1.20 δ.

EXAMPLE 34 3α,5α-Dihydroxy-2β[(3R,S)-3,7-dihydroxy-7-methyl-trans-1-octenyl]-1α-cyclopentane-acetic Acid γ-Lactone, 3,3'-bis(Tetrahydropyran-2-yl Ether) (Formula CXCVIII)

Refer to Chart 34. The Formula-CXCVII 7-oxo lactone (Example 33, 0.500 g.) in 33 ml. of diethyl ther is treated at −78°C. with 2 equivalents of methylmagnesium bromide (0.766 ml. of 2.9 M) added dropwise over one min. The mixture is stirred at −78° for 30 min. more, then treated with an additional 2 equivalents of methylmagnesium bromide at −78° for 2 hr. The mixture is added to 40 ml. of saturated aqueous ammonium chloride and extracted with ether. The organic phase is washed with brine, dried, and concentrated. The concentrate is chromatographed on a HPLC column, eluting with acetonemethylene chloride (1:5) to yield the title compound, 0.391 g., having R_f 0.39 (TLC on silica gel in acetonemethylene chloride (1:3)), NMR peaks at 5.66—5.33, 5.184.81, 4.81—4.47, 4.29—3.16, 2.97—1.29, and 1.16 δ, infrared absorption at 3550, 3000, 1770, 1460, 1440, 1430, 1350, 910, 865, 840, 810, 765, and 735 cm^{-1}, and mass spectral lines at 523.3118, 439, 437, 436, 421, 395, 131, and 85.

EXAMPLE 35 3α,5α-Dihydroxy-2β-[(3R,S)-3,7-dihydroxy-7-methyl-trans-1-octenyl)-1α-cyclopentane acetaldehyde γ-Lactol, 3,3'-bis(Tetrahydropyran-2-yl Ether) (Formula CXCIX).

Refer to Chart 34. The formula-CXCVIII 7-hydroxy-7-methyl lactone (Example 34, 6.98 g.) in 100 ml. of toluene is reduced at −78°C. with diisobutyl aluminum hydride (DIBAL) (25 ml. of 1.5 M in toluene) added dropwise over 13 min. Th mixture is stirred at −78° f r on hr., treated with additional DIBAL (5 ml.), stirred f r 2.25 hr. and again treated with DIBAL (5 ml.). Aft r 0.75 hr. more stirring, the mixture is warm d to −40° ov r 30 min., then cooled to −78° and car fully quenched with saturated aqu ous sodium sulfate. The mixtur is diluted with 850 ml. of diethyl th r, stirred with powdered sodium sulfate (20 g.) until th aluminum salts c agulate, then filt red. Th filtrate is concentrated and then chromatographed on silica gel luting with acetone-methylen chloride (1:2 to 1:1) to yield the title lactol compound, 4.89 g. The product has R_f 0.24 (TLC on silica gel in ac tone-m thylene chloride (1:2)). NMR peaks at 5.77—5.0, 4.86—4.33, 4.33—3.18, 3.11—1.27, and 1.15 δ, infrared absorption

at 3500, 3000, 1750, 1730, 1470, 1450, 1440, 1370, 1340, 1200, 1120, 910, 865, and 810 cm^{-1}, and mass spectral lines at 527.3201, 426, 336, 247, 246, 131, and 85.

EXAMPLE 36 19-Hydroxy-19-methyl-PGF$_2\alpha$, M thyl Ester, 11,15-bis(Tetrahydropyran-2-yl Ether), Mix d C-15 Epimers (Formula CC).

Refer to Chart 34. The Wittig reagent is first pr pared from 4-carboxybutyl triphenylphosphonium bromide (16.19 g.) added to the reaction product of sodium hydride (3.51 g.) and 85 ml. of dimethylsulfoxide previously warmed to 70—75°C. for 1.5 hr. and then cooled to about 25°C. The mixture is stirred at about 25°C. for 25 min., then treated with the formula-CXCIX lactol (Example 35, 4.89 g.) in 35 ml. of dimethylsulfoxide added dropwise over 15 min. and stirred additional 30 min. The mixture is added to one liter of ice-water containing 250 ml. of 2N potassium hydrogen sulfate and then extracted with ether. The organic phase is washed with brine, dried, and concentrated. The product, in 100 ml. of ether and 5 ml. of methanol, is esterified with diazomethane. The solution is concentrated and then chromatographed on a HPLC column eluting with ethyl acetate-Skellysolve B (1:1) to yield the title compounds, 4.08 g. having R_f 0.20 (TLC on silica gel in ethyl acetate-Skellysolve B (2:1)) and 0.60 (TLC on silica gel in acetone-methylene chloride (1:2)), NMR peaks at 5.77—5.29, 4.89—4.60, 4.34—3.16, 3.67, 2.82—1.33, and 1.20δ, and infrared absorption at 3550, 3000, 1740, 1430, 1350, 1200, 1130, 1070, 1020, 970, 900, 865, and 810 cm^{-1}.

EXAMPLE 37 19-Hydroxy-19-methyl-PGF$_2\alpha$, Methyl Ester and its (15R) Epimer (Formula CCI).

Refer to Chart 34. The mixed formula-CC bis(THP ether) compounds (Example 36, 0.590 g.) are hydrolyzed in 33 ml. of acetic acid-water-tetrahydrofuran (20:10:3) at about 25°C. overnight. The mixture is concentrated from toluene and then ethyl acetate. The residue is chromatographed on a HPLC column eluting with acetone-methylene chloride (3:2) to obtain, first, the (15R) title compound, 0.129 g. The (15R) compound has R_f 0.38 and the (15S) compound has R_f 0.27 (TLC on silica gel in acetone-methylene chloride (3:1)). The 15S compound has NMR peaks at 5.75—5.04, 4.32—3.03, 3.65, 2.66—1.31, and 1.17 δ, infrared absorption at 3450, 3000, 1740, 1430, 1360, 1200, 1150, 965, 920, and 900 cm^{-1}, and mass spectral lines at 671.4000, 686, 596, 581, 513, 506, 491, 423, 397, 333, 307, 243, and 217. The (15R) compound has very nearly the same spectral properties.

EXAMPLE 38 19-Hydroxy-19-methyl-PGE$_2$, Methyl Ester, and its (15R) Epimer (Formula CCIII)

Refer to Chart 34. The mixed formula-CC bis(THP ether) PGF$_2\alpha$ compounds (Example 36, 0.602 g.) are oxidized with Jones reagent following the procedure of Example 12, and then are hydrolyzed to replace THP blocking groups following the procedure of Example 37. The mixed C—15 epimers are separated by chromatography on a HPLC column, eluting with acetone-methylene chloride (1:1) to obtain, first, the 15R title compound, 0.119 g. and then the 15S title compound, 0.138 g. The 15R compound has R_f 0.48 and the 15S compound has R_f 0.36 (TLC on silica gel in acetone-methylene chloride (3:1)). The 15S compound has NMR peaks at 5.83—5.02, 4.56—3.33, 3.66, 3.04—1.34, and 1.20 δ, infrared absorption at 3450, 3000, 1740, 1430, 1360, 1300, 1230, 1150, 1070, 1000, 965, 900, and 760 cm^{-1}, and mass spectral lines at 597.3441, 581, 522, 507, 439, 349, 295, and 131. The 15R compound has very nearly the same spectral properties.

EXAMPLE 39 19-Hydroxy-19-methyl-PGF$_2\alpha$, Methyl Ester (Formula CCVI)

Refer to Chart 35. The formula-CLXXVI 9-silyl-11,15-bis(THP ether)-19-keto compound (Example 21, 0.500 g.) in 50 ml. of benzene is treated at about 25°C. with 2.3 equivalents of trimethylaluminum added dropwise over one min. The mixture is stirred for 30 min. and then added to 50 ml. of saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic phase is washed with brine, dried and concentrated. The residue is chromatographed to yield the corresponding 19-hydroxy-19-methyl compound which is then deblocked in tetrahydrofuran-acetic acid-water (3:20:10) to yield the title compound, having the same properties as the product of Example 37.

EXAMPLE 40 15,19-Dimethyl-19-hydroxy-PGF$_2\alpha$, Methyl Ester and its (15R) Epimer (Formula CCVI)

Refer to Charts 30 and 35. As starting material there is used the formula-CXXVI product of Example 15, namely (15R,S)-15-methyl-19,20-didehydro-PGf$_2\alpha$, 11-tetrahydropyranyl ether, methyl ester (Example 15). After saponification and recovery as the free acid, the compound is treated first with the silylating agent, and then with dihydropyran in the presence of pyridine hydrochloride to form a formula-CLXXIV compound of Chart 30. Th reaft r the 15-methyl 19-keto compound of f rmula CLXXVI is prepared using procedures described h r in.

Finally, following th steps of Chart 35, the title compounds are obtain d and separated by silica gel chromatography using proc dur s described herein or known in the art.

EXAMPLE 41 19-Hydroxy-19-methyl-PGF$_1\alpha$, Methyl Est r, and its (15R) Epimer. (Formula CCXIII).

I. R f r to Chart 36. The mix d formula-CC bis (THP ether) f the PGF$_2\alpha$ compounds (Example 36, 1.5 g.) in 60 ml. of ethyl acetate are reduced at C_5—C_6 by hydrogenation at about 25°C. in the presence

of 200 mg. of 5% palladium-on-carbon with slighly over the theory for one equival nt of hydrogen. The solids are filt red off and th filtrat concentrated to yield the corresponding formula-CCXII bis(THP ether) of the $PGF_1\alpha$ compounds having R_f 0.28 (TLC on silica gel in aceton -Sk llysolve B (1:2)).

II. The above compounds are hydrolyzed to the title compounds following the procedure f Example 37, thereaft r separating them by HPLC luting with aceton -methyl ne chloride (1:1). The (15S) title compound has R_f 0.23 (TLC on silica gel in acetone-Skellysolve B (3:1)), NMR peaks at 5.85—5.05, 4.52—3.23, 3.67, 2.68—1.27, and 1.19 δ, infrared absorption at 3450, 3000, 1740, 1440, 1360, 970, and 900 cm^{-1}, and high resolution mass spectral line at 688.4380. The (15R) title compound has R_f 0.29 (TLC on silica gel in acetone-Skellysolve B (3:1)), NMR peaks at 5.85—5.09, 4.33—3.0, 3.65, 2.68—1.28, and 1.20 δ, infrared absorption at 3450, 2950, 1740, 1440, 1360, 970, 905, 825, and 765 cm^{-1}, and high resolution mass spectral line at 688.4394.

EXAMPLE 42 19-Hydroxy-19-methyl-PGE_1, Methyl Ester and its (15R) Epimer. (Formula CCXV).

Refer to Chart 36. The formula-CCXII bis(THP ether) of the $PGF_1\alpha$ compounds (Example 41, 0.900 g.) are oxidized with Jones reagent following the procedure of Example 33 and then are hydrolyzed to replace THP blocking groups following the procedure of Example 37. The mixed C—15 epimers are separated by chromatography on a HPLC column, eluting with acetone-methylene chloride (1:1). The (15S) compound has R_f 0.33 (TLC on silica gel in acetone-methylene chloride (2:1)), NMR peaks at 5.80—5.40, 4.55—3.33, 3.65, 3.00—0.80, and 1.20 δ, infrared absorption at 3450, 2950, 1740, 1430, 1360, 1240, 1150, 1070, 1040, 1000, 965, 910, and 730 cm^{-1}, and high resolution mass spectral line at 599.3590. The (15R) compound has R_f 0.39 (TLC on silica gel in acetone-methylene chloride (2:1)), NMR peaks at 5.85—5.52, 4.38—3.58, 3.67, 3.58—2.81, 2.81—1.03, and 1.20 δ, infrared absorption at 3450, 2950, 1740, 1430, 1260, 1150, 1070, and 965 cm^{-1}, and high resolution mass spectral line at 628.3900.

EXAMPLE 43 19-hydroxy-19-methyl-13,14-dihydro-(15R)-PGE_1, Methyl Ester.

The formula-CCXV 19-hydroxy-19-methyl-(15R)-PGE_1, methyl ester (Example 42, 0.148 g.) is hydrogenated again over 5% palladium-on-carbon, following the procedure of Example 41. The product is chromatographed by HPLC, eluting with acetone-methylene chloride (1:2) to yield the title compound, 0.031 g. having R_f 0.35 (TLC on silica gel in acetone-methylene chloride (2:1)), NMR peaks at 4.44—3.60, 3.66, 3.46—3.08, 2.96—1.08, and 1.21 δ, infrared absorption at 3500, 3000, 1740, 1430, 1270, and 1150, and high resolution mass spectral peak at 601.3797.

EXAMPLE 44 19-Hydroxy-19-methyl-13,14-dihydro-(15S)-PGE_1, Methyl Ester

The formula-CCXIII 19-hydroxy-19-methyl-PGE_1, methyl ester (Example 42, 0.179 g.) is converted to its bis(THP ether) and hydrogenated again following the procedure of Example 41. Thereafter the THP groups are replaced by hydrolysis and the product chromatographed by HPLC eluting with acetone-methylene chloride (2:3) to yield the title compound, 0.031 g. The compound has R_f 0.41 (TLC on silica gel in acetone-methylene chloride (2:1)), and spectral data similar to that for the 15R epimer (Example 43).

EXAMPLE 45 2-Decarboxy-2-hydroxymethyl-19-hydroxy-19-methyl-$PGF_2\alpha$, 11,15-bis(tetrahydropyran-2-yl ether), Mixed C—15 Epimers. (Formula CCLXVII).

Refer to Chart 46. The formula-CCLXVI 19-hydroxy-19-methyl-$PGF_2\alpha$, methyl ester, 11,15-bis(tetrahydropyran-2-yl ether) (Example 36, 1.98 g.) in 65 ml. of ether is added dropwise in 20 min. to a stirred suspension of lithium aluminum hydride (0.530 g.) in 130 ml. of ether at about 25°C. The mixture is stirred for 2.5 hr. and then quenched by careful addition of saturated sodium sulfate solution. There is then added 400 ml. of ether and 10—12 g. of powdered anhydrous sodium sulfate and, after about 30 min. stirring, the solids are filtered off and the filtrate is concentrated to yield the title compounds. They have R_f 0.30 (TLC on silica gel in ethyl acetate) and NMR peaks at 5.82—5.00, 4.86—4.57, 4.36—3.17, 2.88—1.31, and 1.19 δ.

EXAMPLE 46 2-Decarboxy-2-hydroxymethyl-19-hydroxy-19-methyl-$PGF_2\alpha$ and its (15R) Epimer. (Formula CCLXVIII).

Refer to Chart 46. Following the procedures of Example 37 the bis(THP ether) compounds of Example 45 are hydrolyzed and chromatographed to yield the title compounds.

EXAMPLE 47 2-D carboxy-2-hydroxymethyl-19-hydroxy-19-methyl-PGE_2 and its (15R) Epimer. (Formula CCLXXI).

I. Ref r to Chart 46. There are first prepared th formula-CCLXIX m nosilyl compounds. The formula-CCLXVII bis(THP ether) compounds (Example 45, 1.88 g.) in 18 ml. of dimethylformamide are treat d at 0°C. with imidazole (0.332 g.) and t-butyldimethylsilyl chl ride (0.529 g.) After 40 min. there is added ice-water (200 ml.) and ether (200 ml.) and the layers are separated. The organic phase is washed with water, dried, and concentrated. The residue is chromatographed on a HPLC column,

eluting with ethyl acetate-Skellysolve B [illegible] formula CCLXIX [illegible] 1.8 g, having R_f 0.27 (TLC on silica gel [illegible] methylene chloride [illegible]).

II. The above compounds are oxidized with Collins reagent prepared from pyridine (3.05 g) in 65 ml of methylene chloride and chromium trioxide (1.93 g). The above compounds (1.8 g) in 40 ml of methylene chloride are added dropwise [illegible] to the reagent at 0°C. Thereafter the mixture is stirred at about 25°C for one [illegible] and filtered. The filtrate is concentrated to yield the title compounds as the 11,15-bis(THP) [illegible] of formula CCLXX. The blocking groups are replaced by hydrogen [illegible] tetrahydrofuran (20:10:3) at about 25°C for [illegible] and [illegible] at about 40°C [illegible]. The product [illegible] separated by HPLC [illegible] (15R) compound 0.331 g [illegible] peaks at 5.88 [illegible] 5.06 4.15 [illegible] 3.20 [illegible] 2.84 [illegible] 1730, 1360, 1230, 1160, 1080, 1040 [illegible] 900, 840 [illegible] 641 [illegible] 551 482, 476 392 [illegible] 131. The (15S) [illegible] NMR peaks at 5.98 [illegible] 5.03 4.66 [illegible] 3.04 [illegible] 1.23 and 1.20 δ; [illegible] (15R) compound.

EXAMPLE 48 2-Decarboxy-2-hydroxymethyl-19-hydroxy-19-methyl-PGE [illegible] and its (15R) Epimers

Following the procedures of Examples 45 and 47, the mixed 15-epimers of 19-hydroxy-19-methyl-PGF [illegible] methyl ester, as their 11,15-bis(THP) ethers (Example 41 [illegible] 0.726 g) are reduced first to their 2-decarboxy-2-hydroxymethyl [illegible]. There are next prepared the corresponding mono-silyl bis-THP ether compounds which are oxidized with Collins reagent to form the PGE compounds. Finally the blocking groups are replaced [illegible] the title compounds. The (15S) [illegible] 0.130 g [illegible] R_f 0.35 [illegible] methylene chloride [illegible] NMR peaks at 5.84 [illegible] 3.05 [illegible] absorption at 3400 2950 1740 1460 1370 [illegible] 900 [illegible] high resolution mass spectral peak at [illegible] NMR peaks [illegible] 5.82 [illegible] 3.03 [illegible] 1.33 [illegible] (15R) compound.

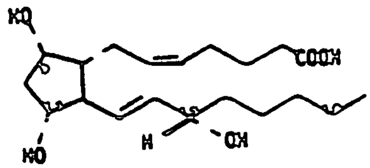
eluting with ethyl acetate-Skellysolve B (2:3) to yield the mixed formula-CCLXIX monosilyl compounds, 1.8 g., having R_f 0.27 (TLC n silica gel in acet ne-methylen chloride (1:6)).

II. The above compounds are oxidiz d with Collins reagent prepared from pyridine (3.05 g.) in 65 ml. of methylene chloride and chromic anhydride (1.93 g.). The above compounds (1.8 g.) in 40 ml. of methylen chloride are add d dropwise over 8 min. t the reagent at 0°C. Thereafter the mixture is stirred at about 25°C. f r one hr., diluted with ether and filtered. The filtrate is concentrated to yield the title compounds as their 1-silyl, 11,15-bis(THP ether) derivatives of formula CCLXX. The blocking groups are replaced by hydrolysis in 66 ml. of acetic acid-water-tetrahydrofuran (20:10:3) at about 25°C. for 16 hr. and finally at about 40°C. for 4 hr. The products are separated by HPLC chromatography, eluting with acetone-methylene chloride (1:1) to yield the (15R) compound, 0.332 g., having R_f 0.20 (in acetone-methylene chloride (2:1)) NMR peaks at 5.88—5.08, 4.483.36, 3.20—2.84, 2.78—1.35, and 1.20 δ, infrared absorption at 3450, 2950, 1730, 1360, 1230, 1150, 1080, 1040, 985, 920, 840, 820, and 760 cm^{-1}, and mass spectral lines at 641.566, 551, 483, 476, 393, 339, and 131. The (15S) compound, 0.417 g., has R_f 0.13, NMR peaks at 5.98—5.03, 4.66—3.21, 3.04—1.33 and 1.20 δ, and infrared and mass spectral properties similar to those of the (15R) compound.

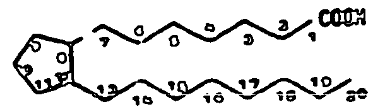
EXAMPLE 48 2-Decarboxy-2-hydroxymethyl-19-hydroxy-19-methyl-PGE$_1$ and its (15R) Epimers.

Following the procedures of Examples 45 and 47, the mixed 15-epimers of 19-hydroxy-19-methyl-PGF$_1\alpha$, methyl ester, as their 11,15-bis(THP ethers) (Example 41—1, 0.726 g.) are reduced first to their 2-decarboxy-2-hydroxymethyl counterparts. There are next prepared the corresponding mono-silyl bis(THP ether) compounds, which are oxidized with Collins reagent to form the PGE compounds. Finally, the blocking groups are replaced by hydrolysis to yield the title compounds. The (15R) compound, 0.130 g., has R_f 0.35 (TLC on silica gel in acetone-methylene chloride (1:1)). NMR peaks at 5.84—5.29, 4.83—3.05, 2.95—1.96, and 1.17 δ, infrared absorption at 3400, 2950, 1740, 1460, 1370, 1230, 1150, 1070, 970, 900, and 765 cm^{-1}, and high resolution mass spectral peak at 643.4037. The (15S) compound, 0.115 g., has R_f 0.26, NMR peaks at 5.82—5.26, 4.92—3.03, 2.93—1.25, and 1.15 δ, and infrared absorption similar to the 15(R) compound.

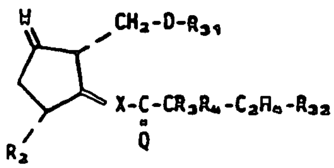
FORMULAS



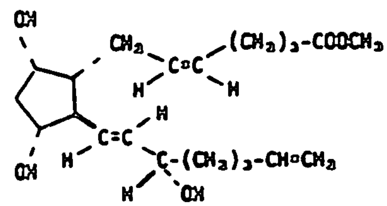
I



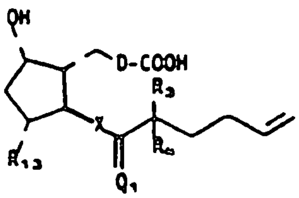
II



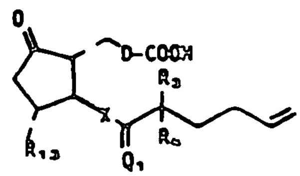
III



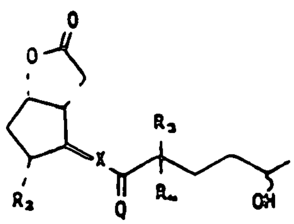
VII



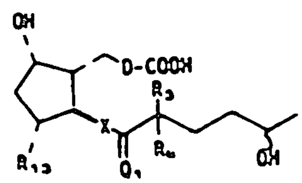
IX



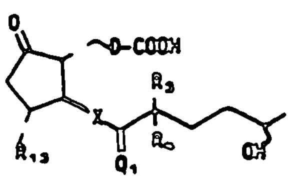
XI



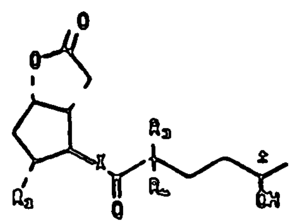
XV



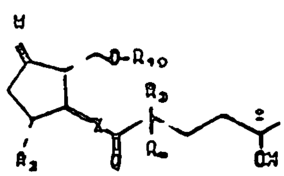
XVI



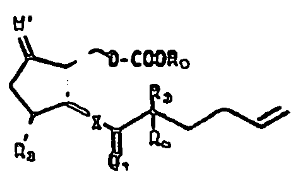
XVII



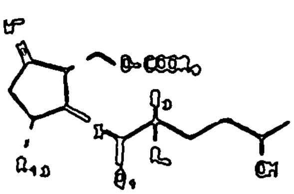
XVa



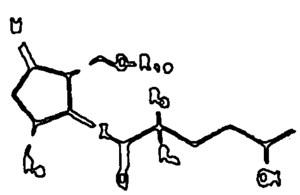
IVa



XVIII

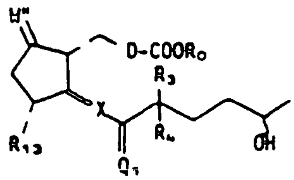


XIX

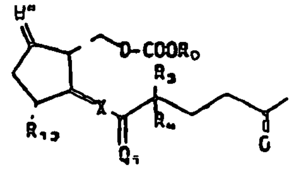


XX

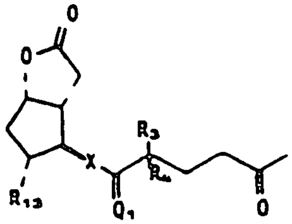
FORMULAS (continued)



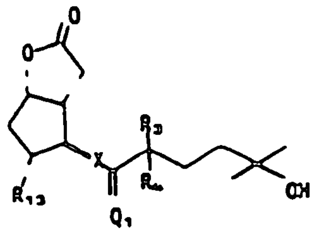
XXI



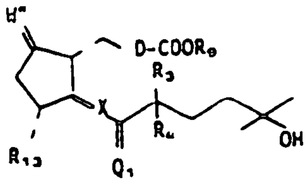
XXII



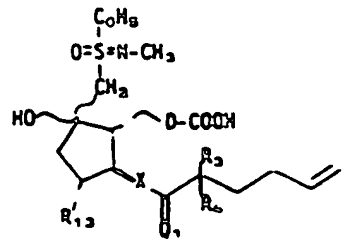
XXIII



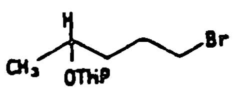
XXIV



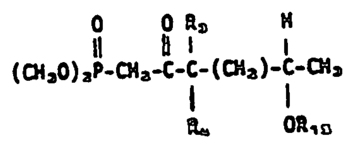
XXV



LVI

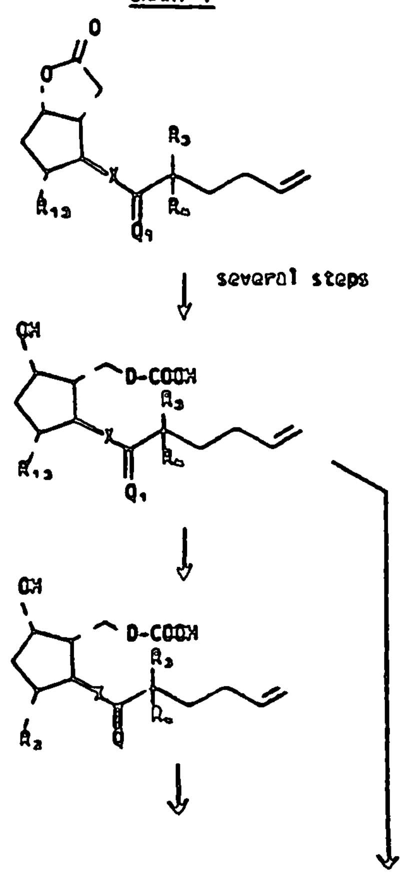


CLI



CLXI

CHART 1

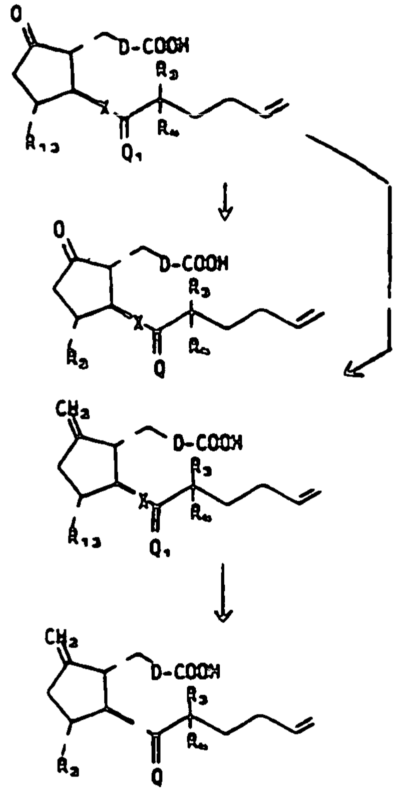


VIII

IX

X

CHART 1 (continued)



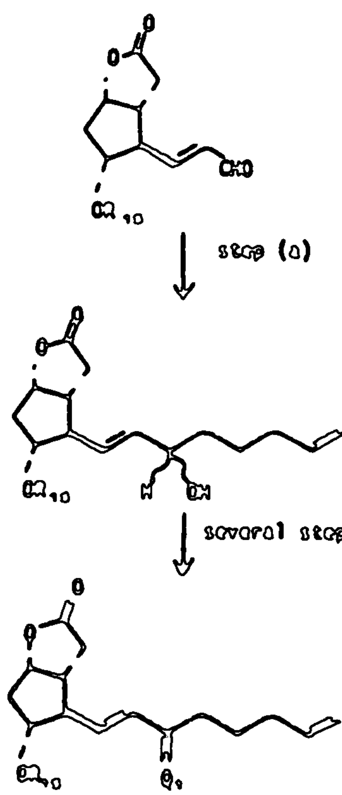
XI

XII

XIII

XIV

CHART 2

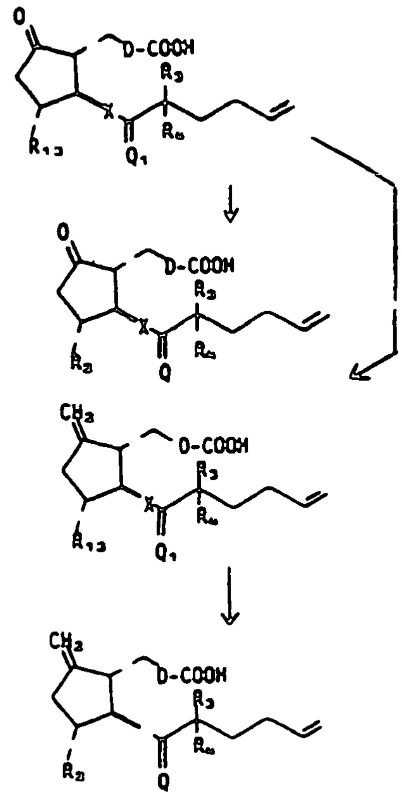


XXVI

XXVII

XXVIII

CHART 1 (continued)



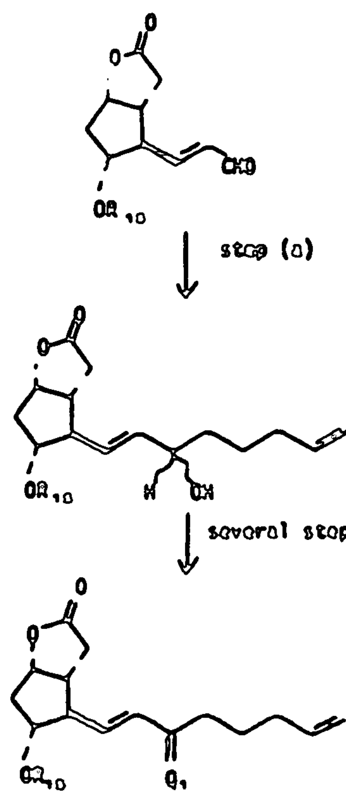
XI

XII

XIII

XIV

CHART 2

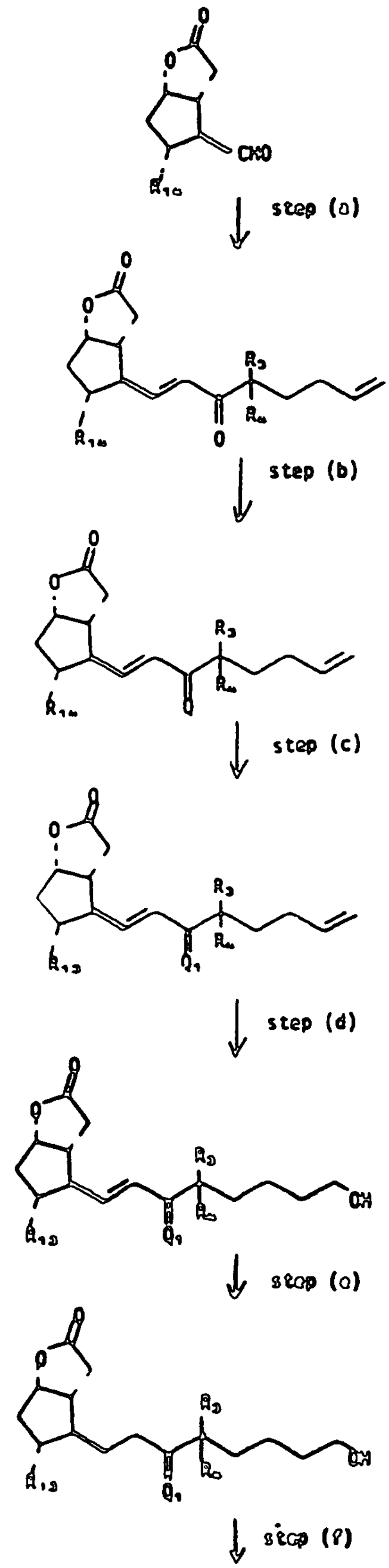


XXVI

XXVII

XXVIII

CHART 3



XXXVII

XXXVIII

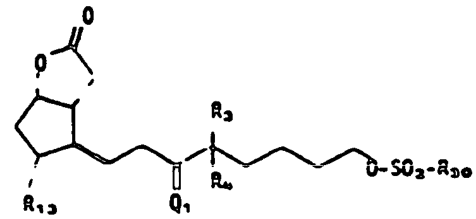
XXXIX

XL

XLI

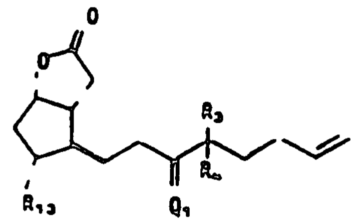
XLII

CHART 3 (continued)



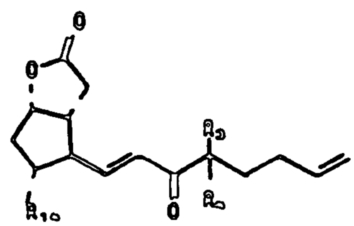
XLIII

step (g)

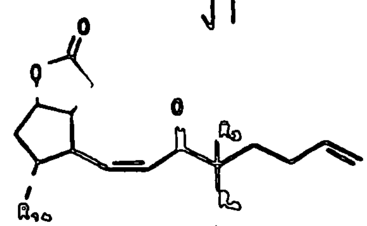


XLIV

CHART 4

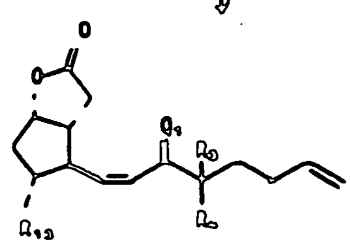


XXXVIII



XLV

several steps



XLVI

CHART 5

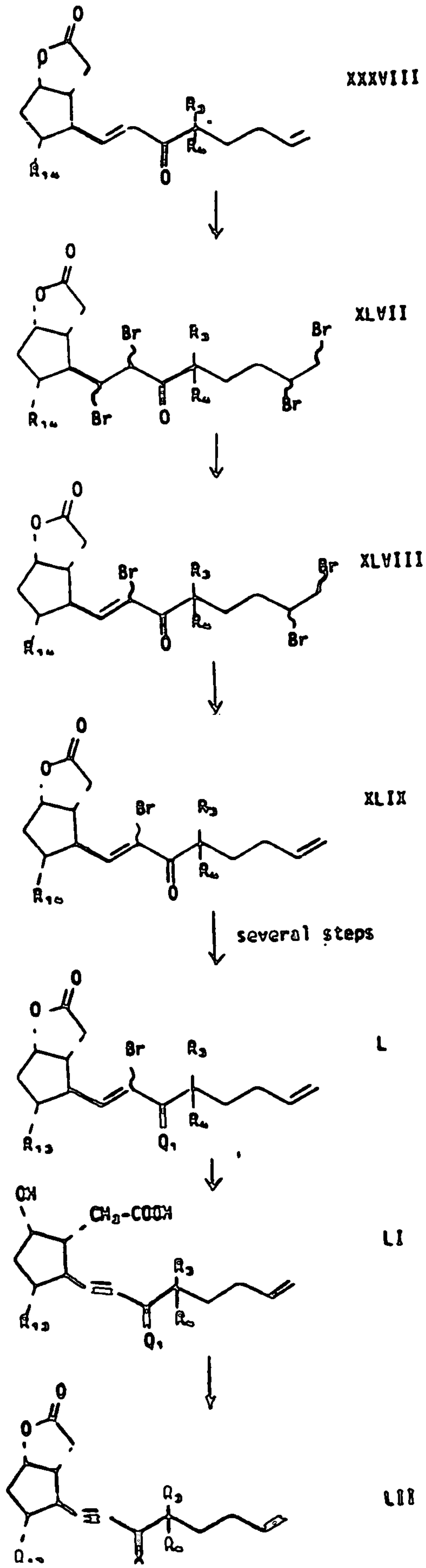
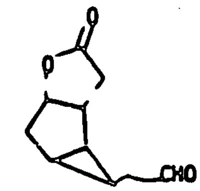
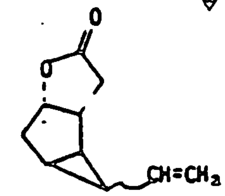


CHART 6



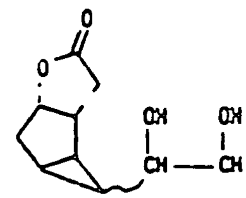
XXIX

step (a)



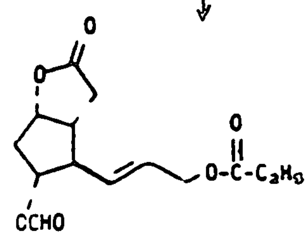
XXX

step (b)



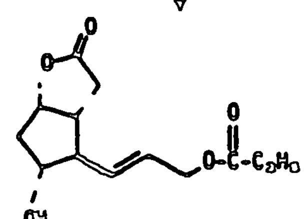
XXXI

step (c)



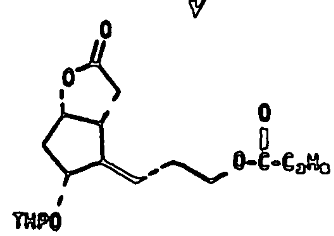
XXXII

step (d)



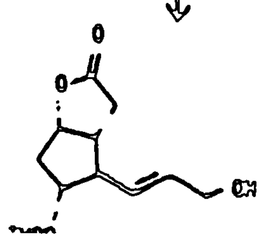
XXXIII

step (e)



XXXIV

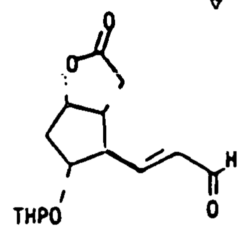
step (f)



XXXV

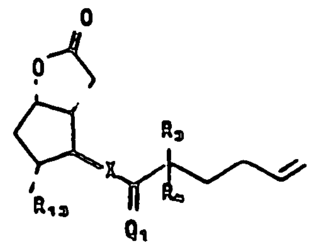
CHART 6 (continued)

step (g)



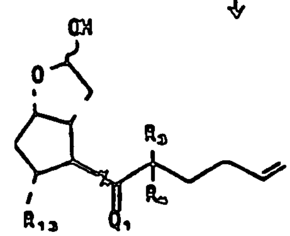
XXXVI

CHART 7



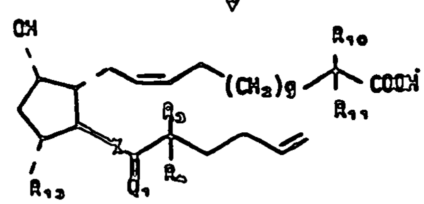
VIII

step (a)



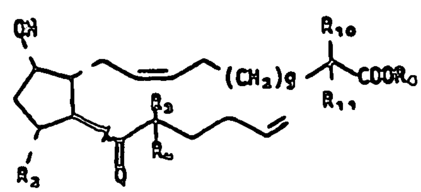
LIII

step (b)



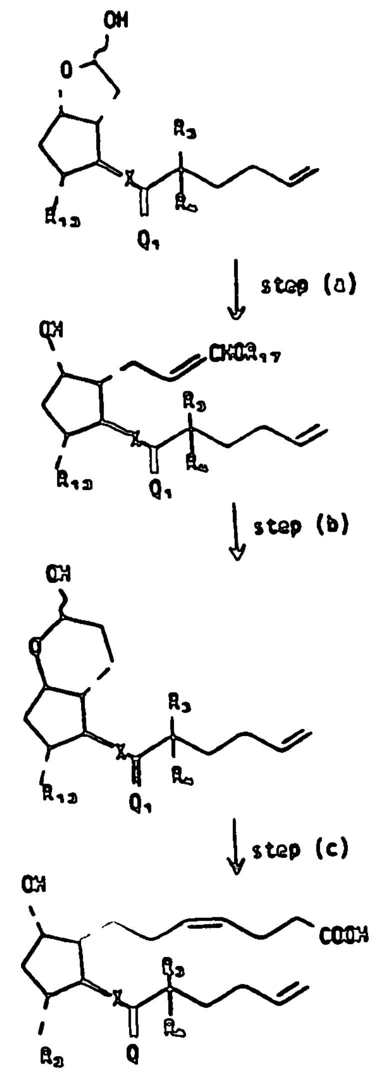
LIV

step (c)



LV

CHART 8



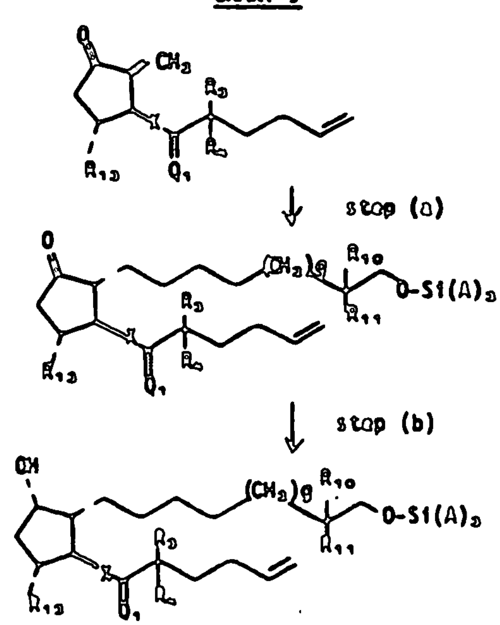
LIII

LVII

LVIII

LIX

CHART 9



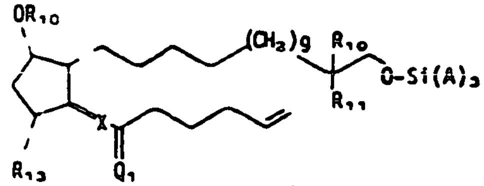
LX

LXI

LXII

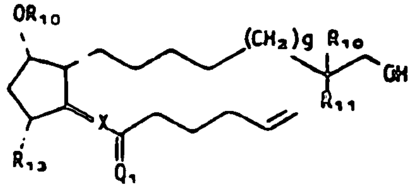
CHART 9 (continued)

step (c)



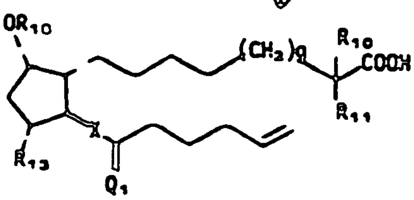
LXIII

step (d)



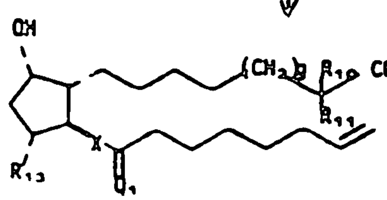
LXIV

step (e)

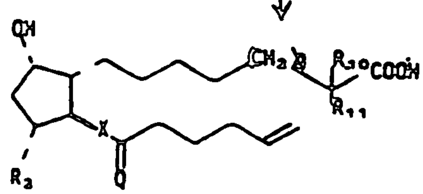


LXV

step (f)

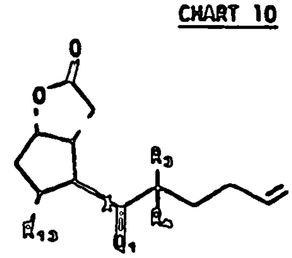


step (g)



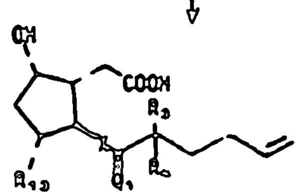
LXVII

CHART 10



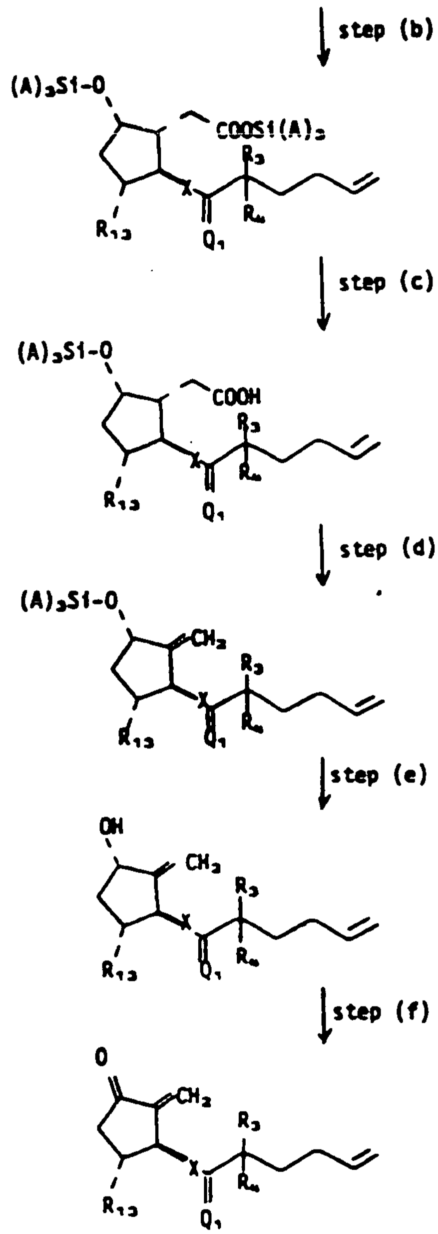
VIII

step (a)



LXVIII

CHART 10 (continued)



LXIX

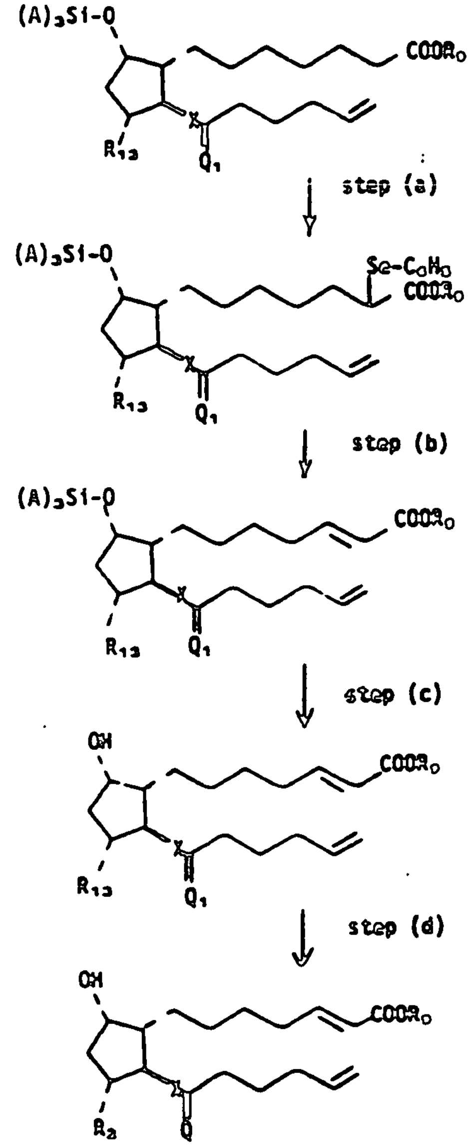
LXX

LXXI

LXXII

LX

CHART 11



LXXIII

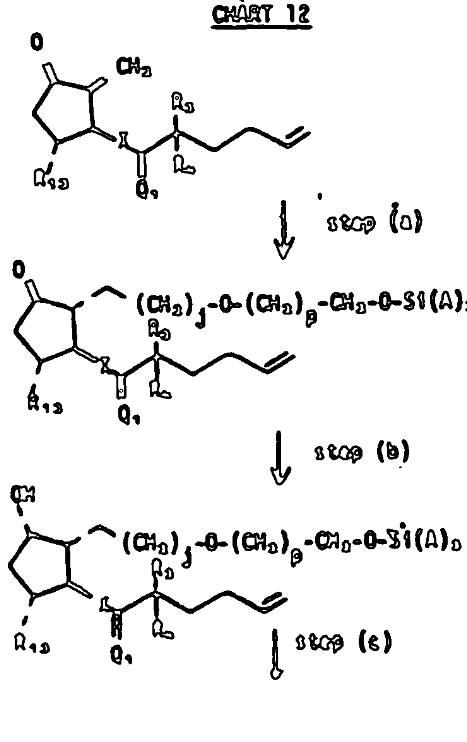
LXXIV

LXXV

LXXVI

LXXVII

CHART 12



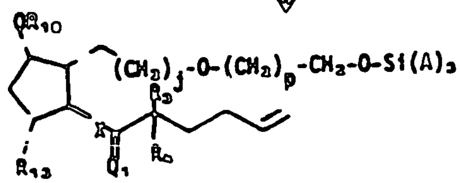
LX

LXXVIII

LXXIX

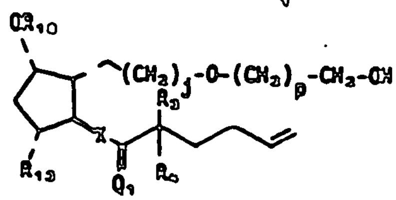
CHART 12 (continued)

↓ step (c)



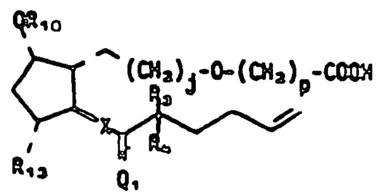
LXXX

↓ step (d)



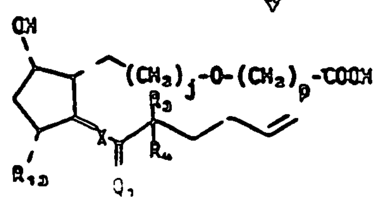
LXXXI

↓ step (e)



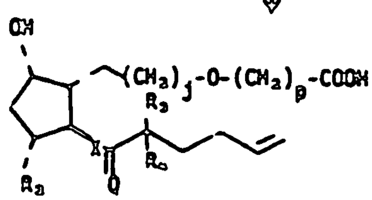
LXXXII

↓ step (f)



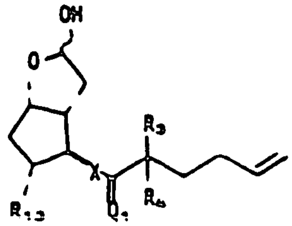
LXXXIII

↓ step (g)



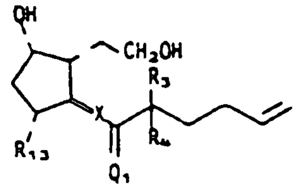
LXXXIV

CHART 13



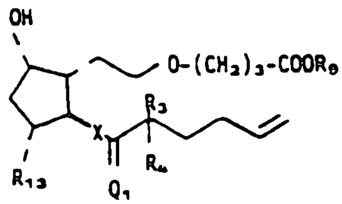
LIII

step (a)



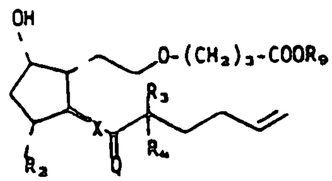
LXXXV

step (b)



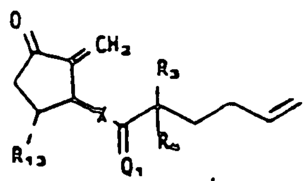
LXXXVI

step (c)



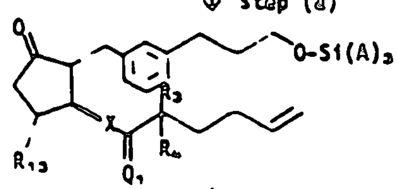
LXXXVII

CHART 14



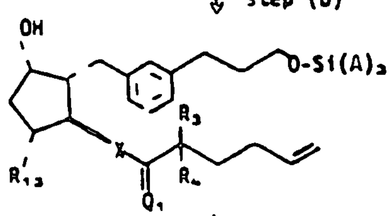
LX

step (a)



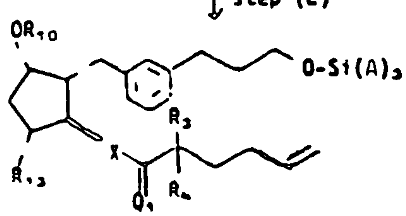
LXXXVIII

step (b)



LXXXIX

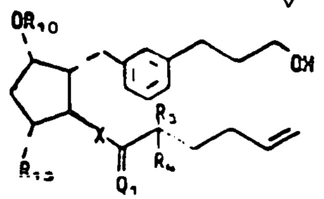
step (c)



XC

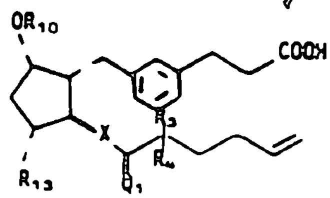
CHART 14 (continued)

↓ step (d)



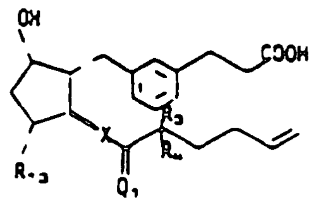
XCI

↓ step (e)



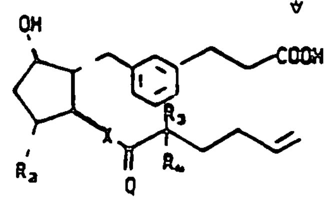
XCII

↓ step (f)



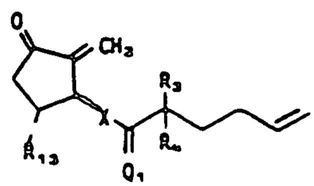
XCIII

↓ step (g)



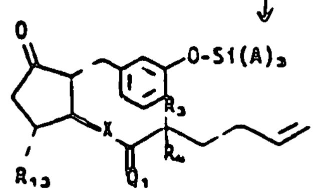
XCIV

CHART 15



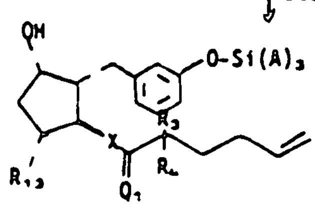
LX

↓ step (a)



XCV

↓ step (b)



XCVI

↓ step (c)

CHART 15 (continued)

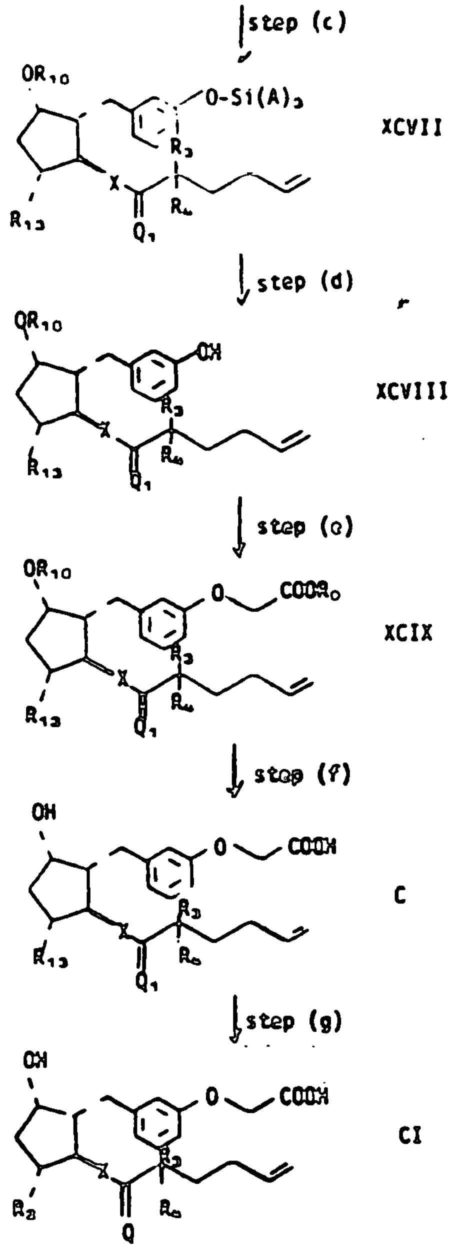
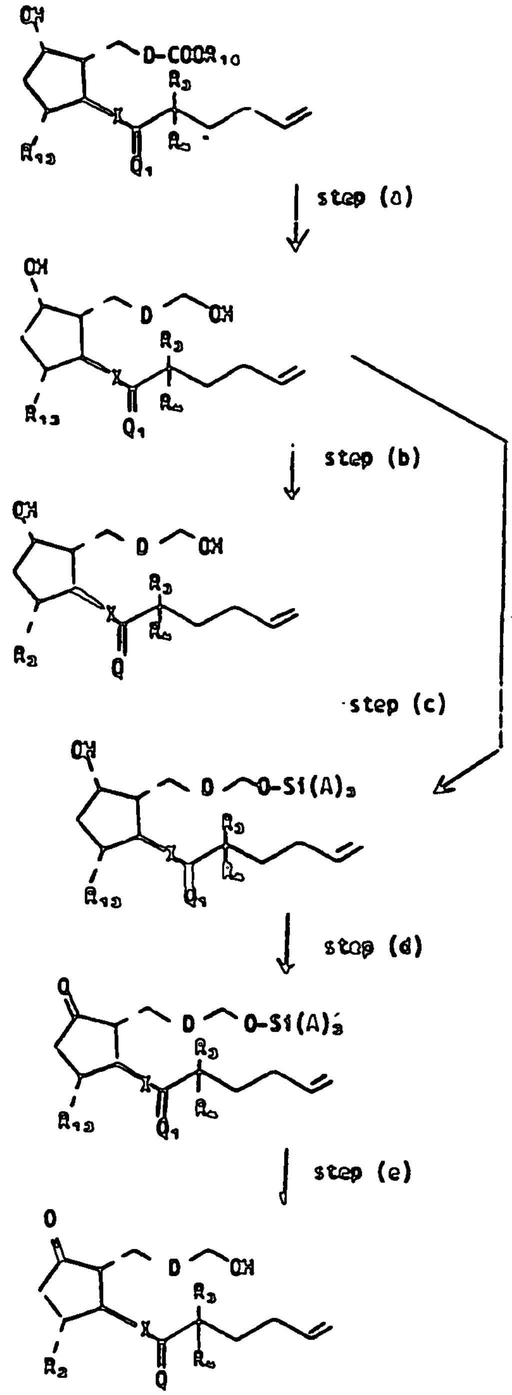


CHART 16



CII

CIII

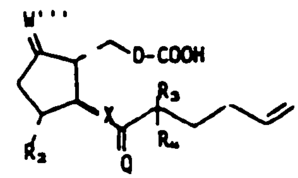
CIV

CV

CVI

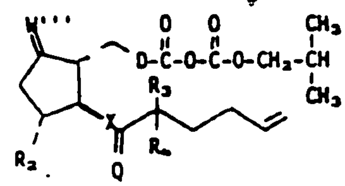
CVII

CHART 17



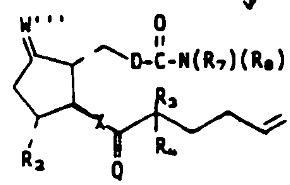
CVIII

↓ step (a)



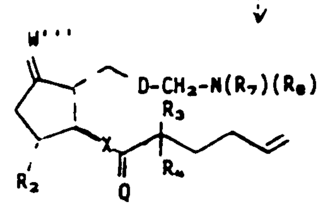
CIX

↓ step (b)



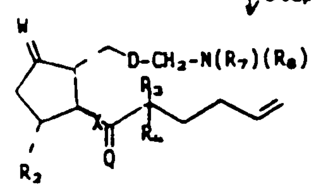
CX

↓ step (c)



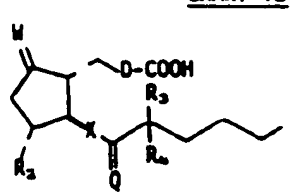
CXI

↓ step (d)



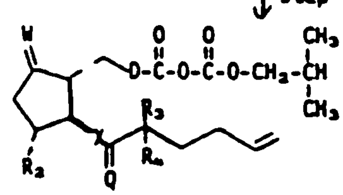
CXII

CHART 18



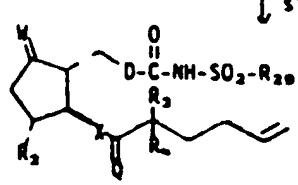
CXIII

↓ step (a)



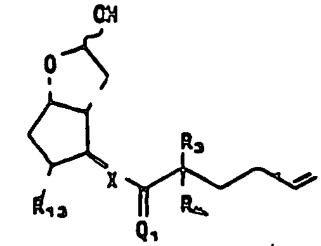
CXIV

↓ step (b)



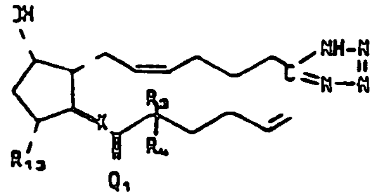
CXV

CHART 19



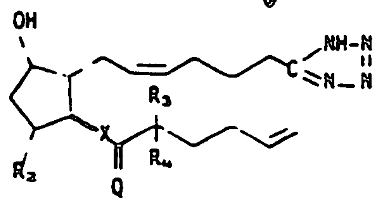
LIII

step (a)



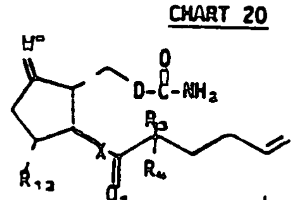
CXVI

step (b)



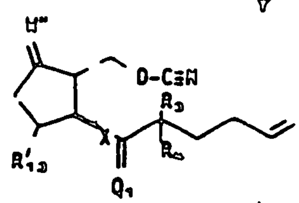
CXVII

CHART 20



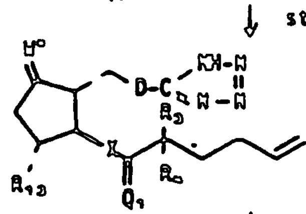
CXVIII

step (a)



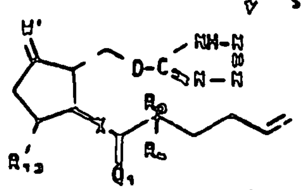
CXIX

step (b)



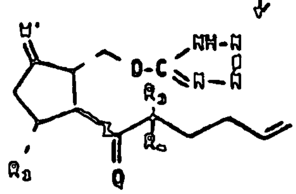
CXX

step (c)



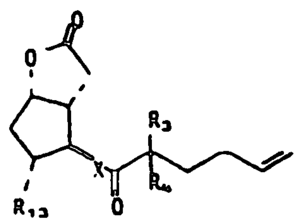
CXXI

step (d)



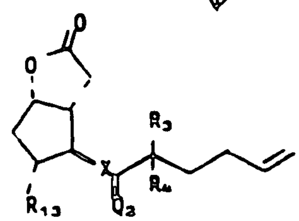
CXXII

CHART 21



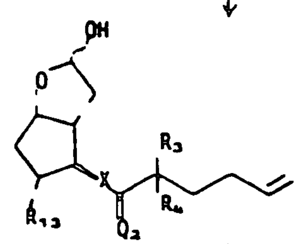
CXXIII

step (a)



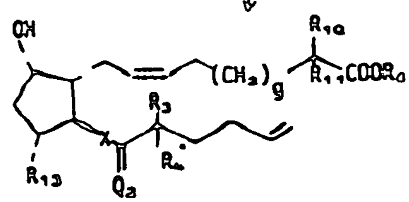
CXXIV

step (b)



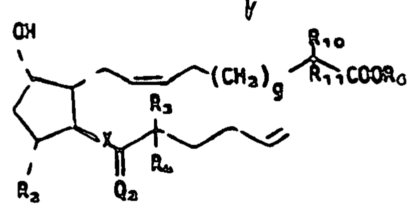
CXXV

step (c)



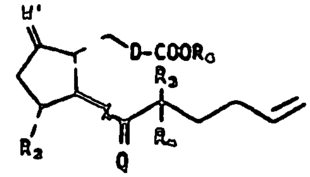
CXXVI

step (d)

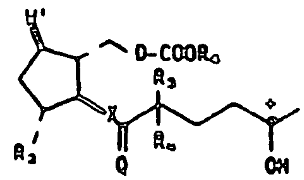


LV

CHART 22

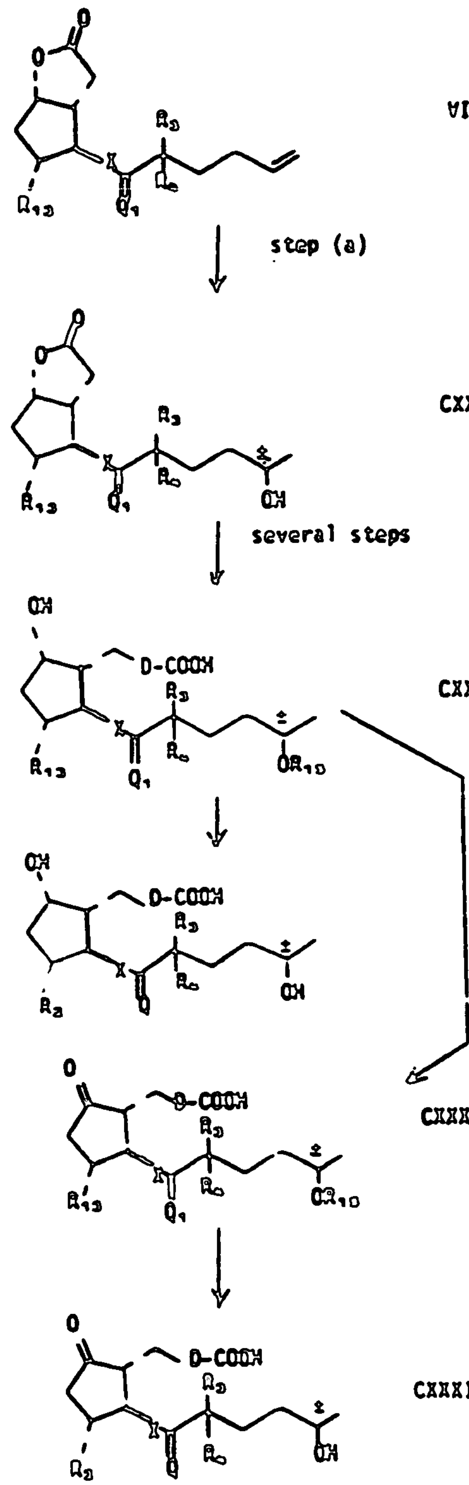


CXXVII



CXXVIII

CHART 23



VIII

CXXIX

CXXX

CXXXI

CXXXII

CXXXIII

CHART 24

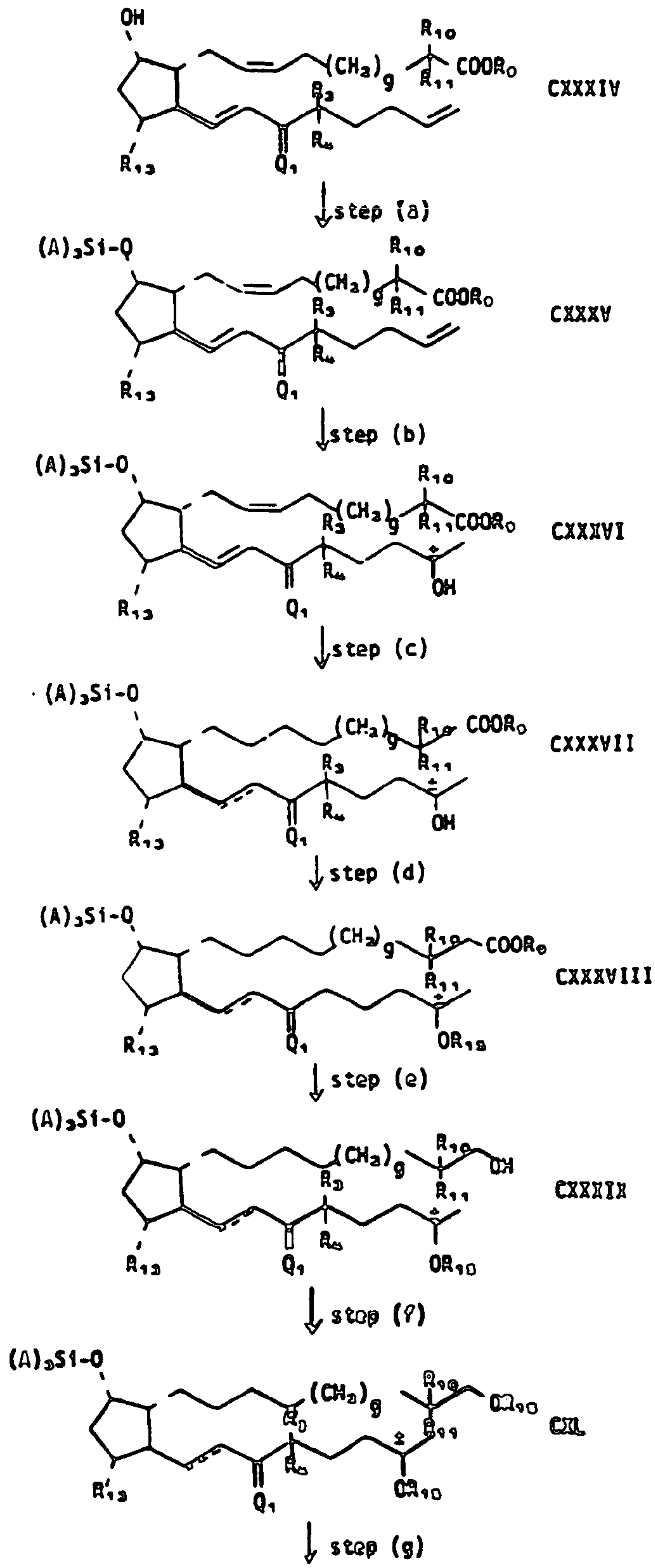
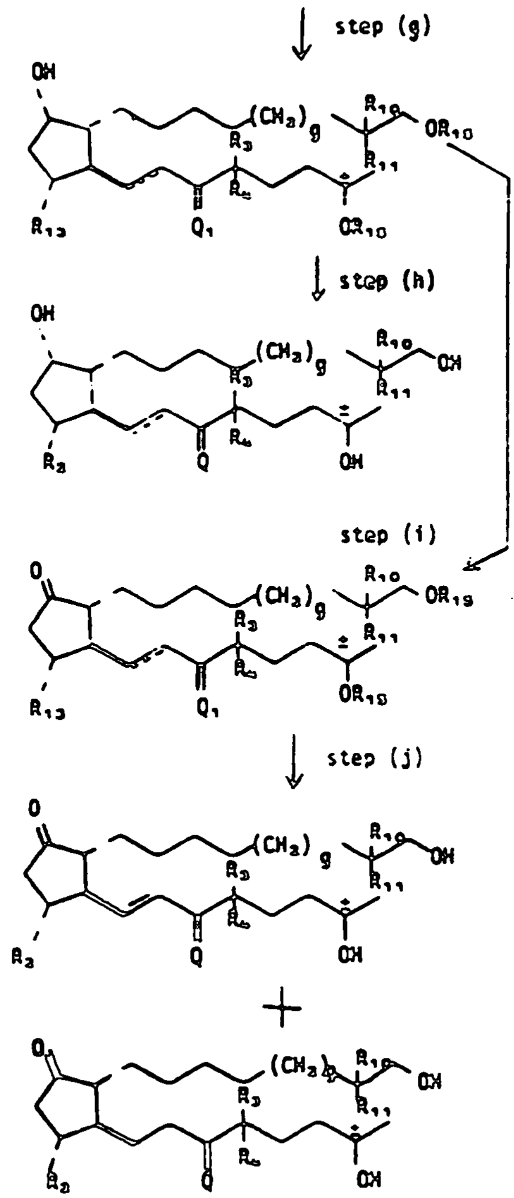

CXXXIV
step (a)
CXXXV
step (b)
CXXXVI
step (c)
CXXXVII
step (d)
CXXXVIII
step (e)
CXXXIX
step (f)
CXL
step (g)

CHART 24 (continued)



CXLI

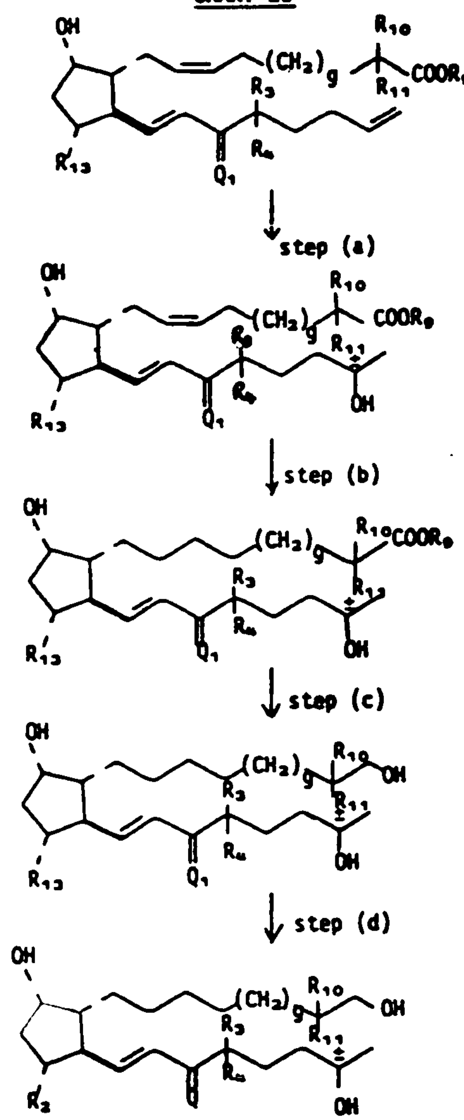
CXLII

CXLIII

CXLIV

CXLV

CHART 25



CXLVI

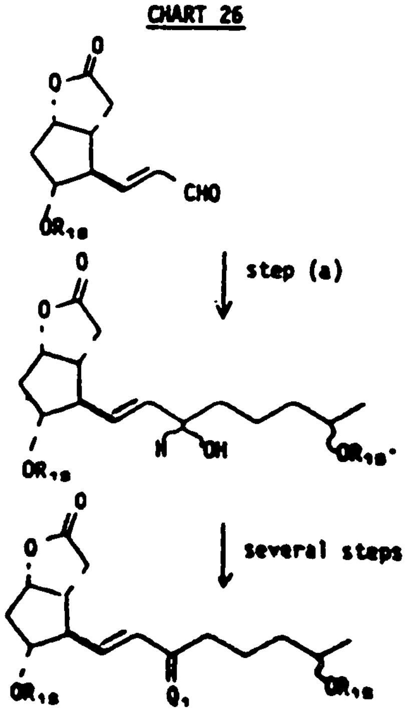
CXLVII

CXLVIII

CXLIX

CL

CHART 26

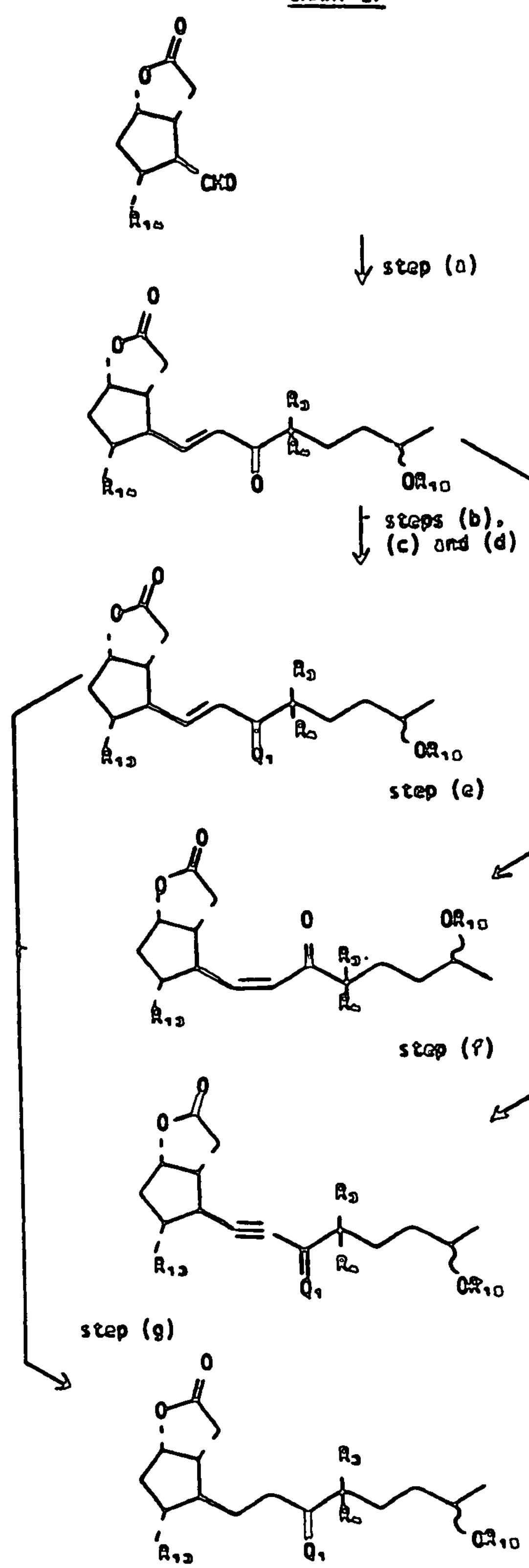


XXVI

CLII

CLIII

CHART 27



XXXVII

CLIV

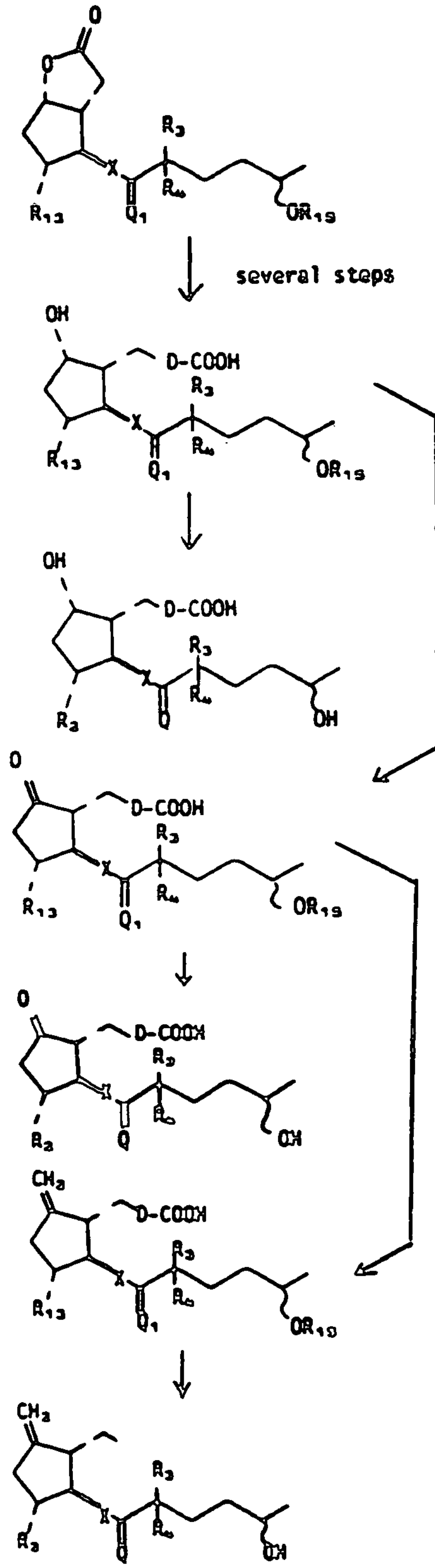
CLVI

CLVII

CLVIII

CLIX

CHART 28



CLXII

CLXIII

CLXIV

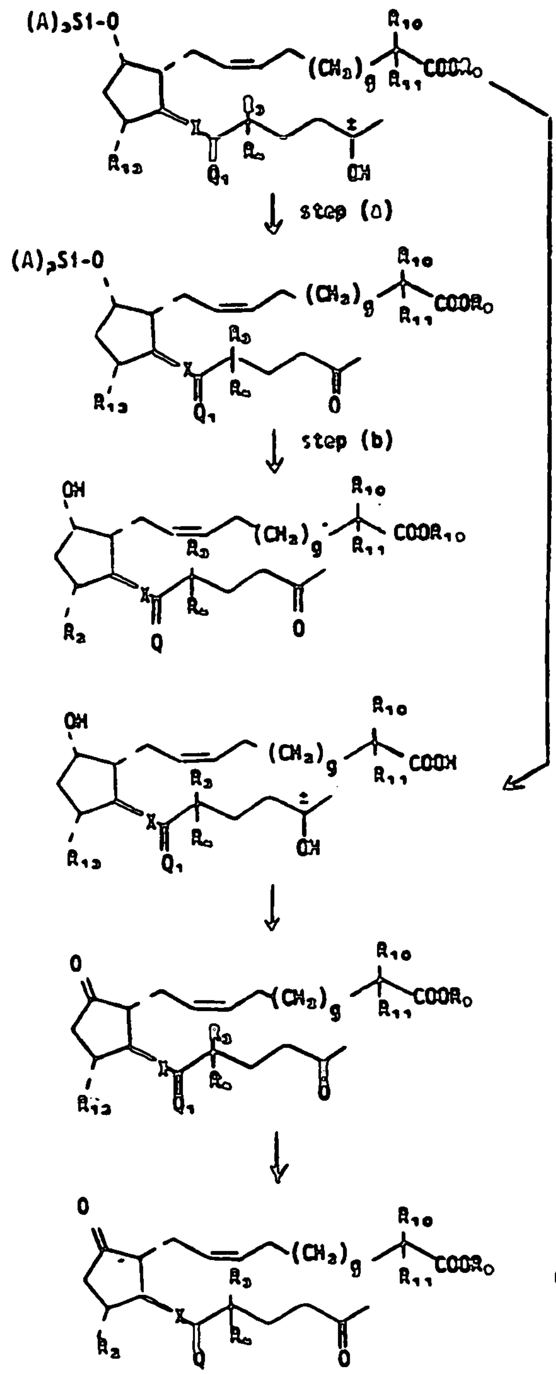
CLXV

CLXVI

CLXVII

CLXVIII

CHART 29



CXXXVI

CLXIX

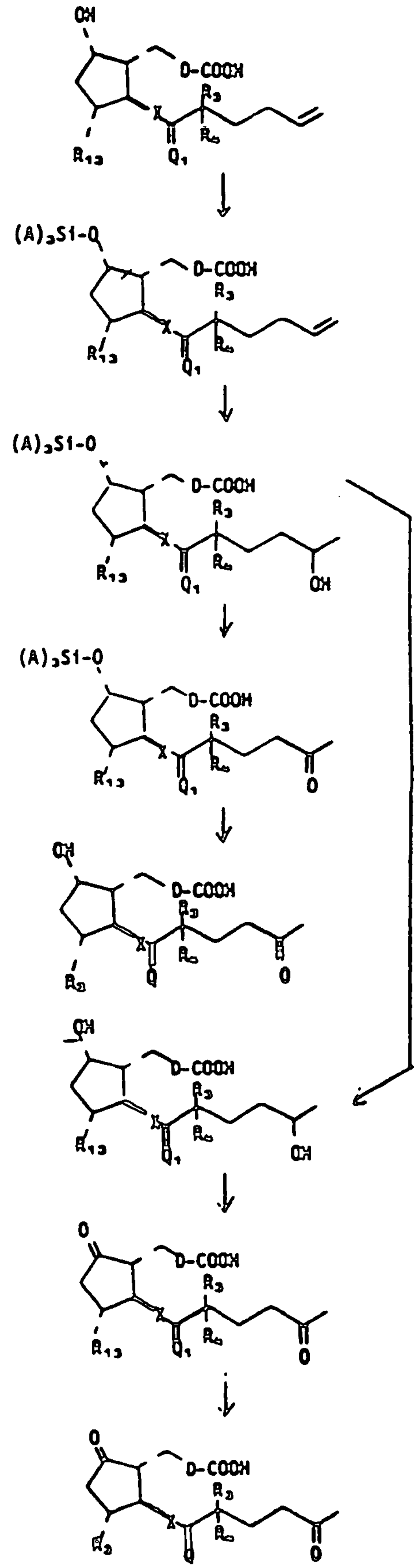
CLXX

CLXXI

CLXXII

CLXXIII

CHART 30



IX

CLXXIV

CLXXV

CLXXVI

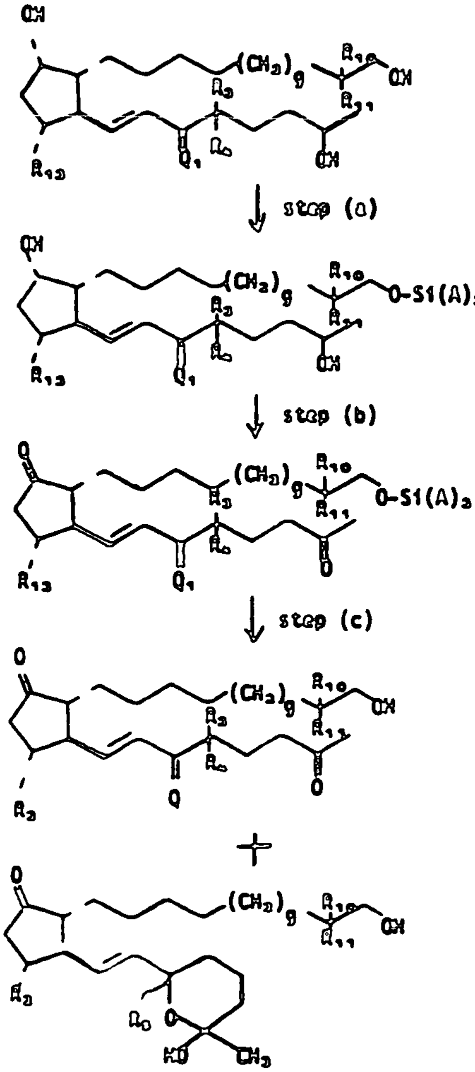
CLXXVII

CLXXVIII

CLXXIX

CLXXX

CHART 31



CXLIX

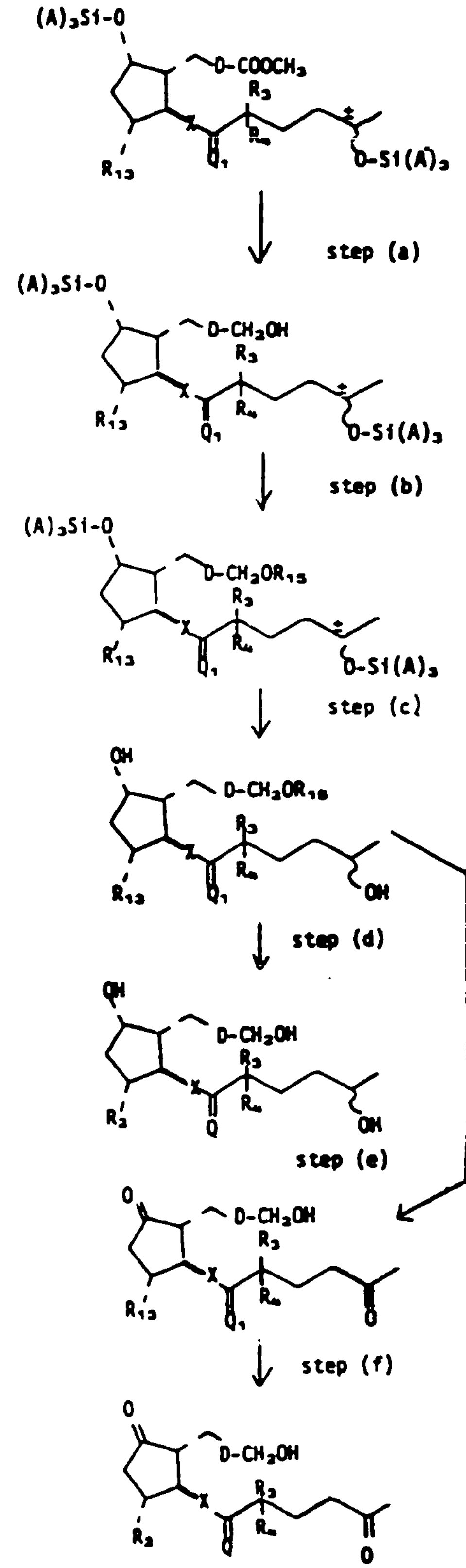
CLXXXI

CLXXXII

CLXXXIII

CLXXXIV

CHART 32



CLXXXV

CLXXXVI

CLXXXVII

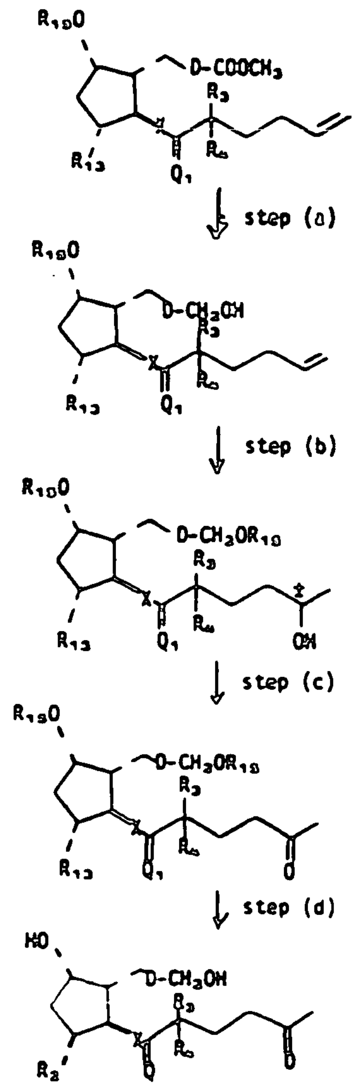
CLXXXVIII

CLXXXIX

CXC

CXCI

CHART 33



CXCII

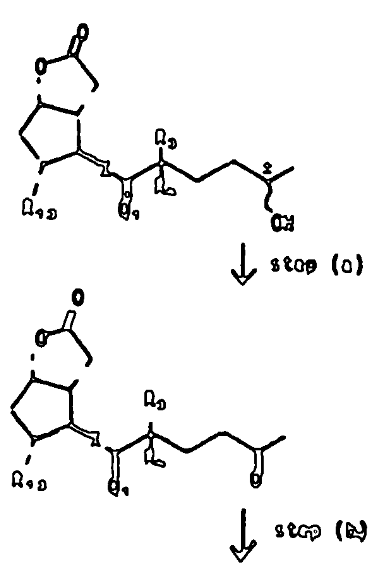
CXCIII

CXCIV

CXCV

CXCVI

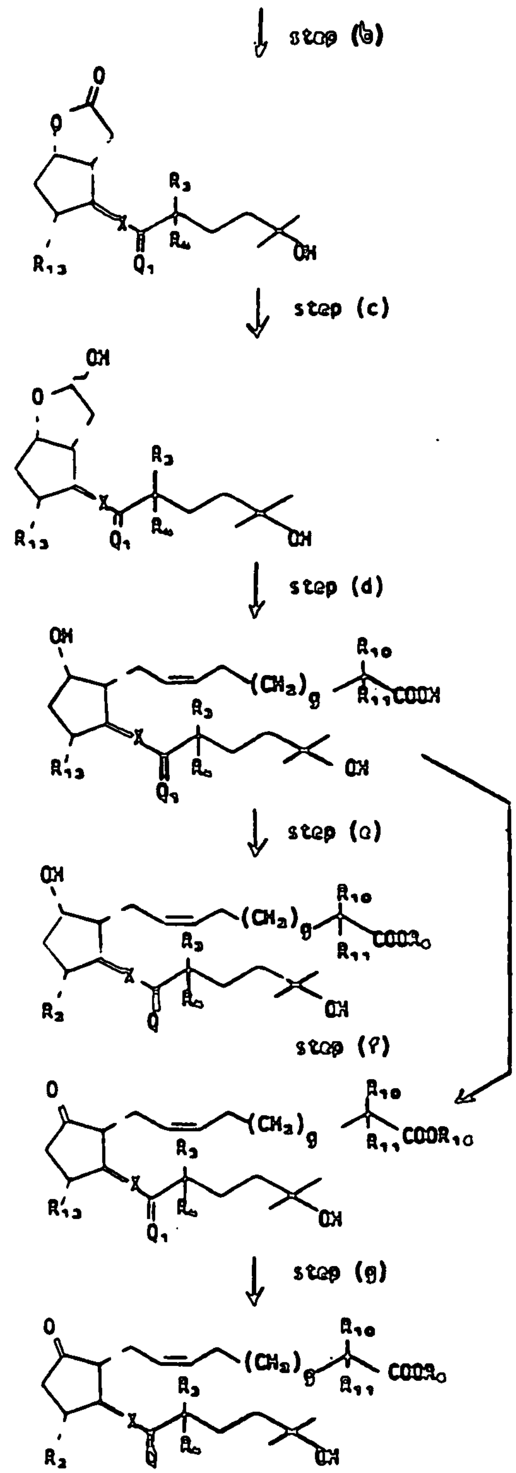
CHART 34



CXXIX

CXCVII

CHART 34 (continued)



CXCVIII

CXCIX

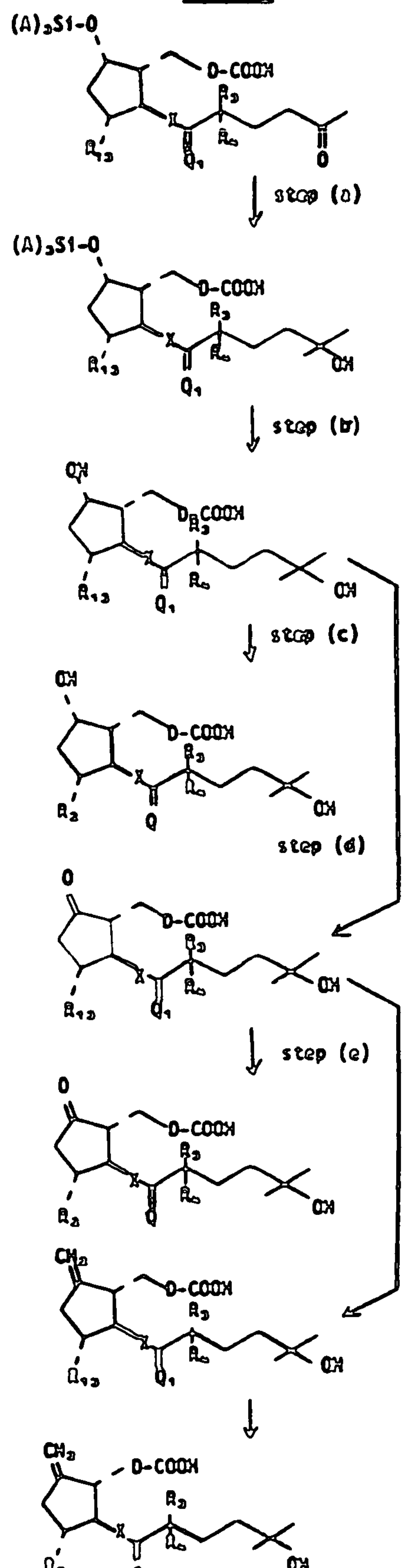
CC

CCI

CCII

CCIII

CHART 35



CLXXVI

CCIV

CCV

CCVI

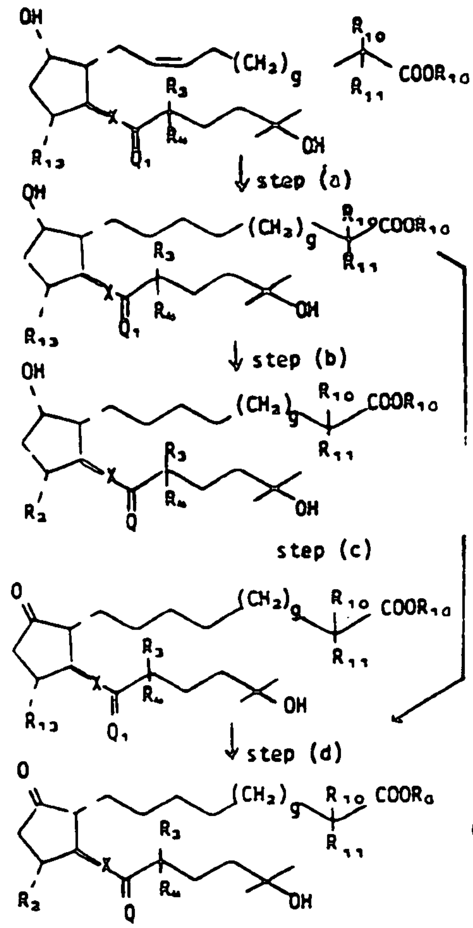
CCVII

CCVIII

CCIX

CCX

CHART 36



CCXI

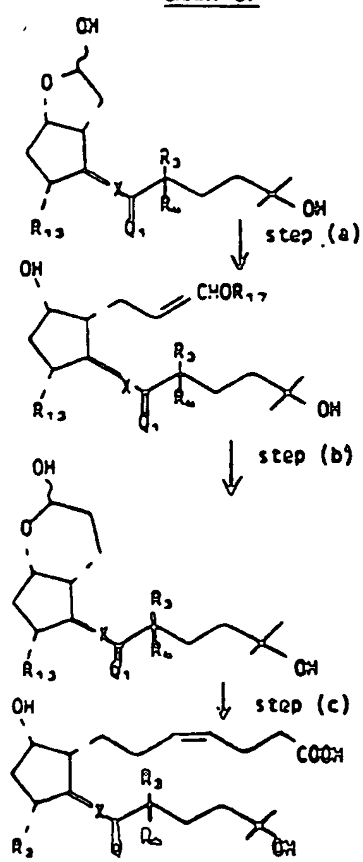
CCXII

CCXIII

CCXIV

CCXV

CHART 37



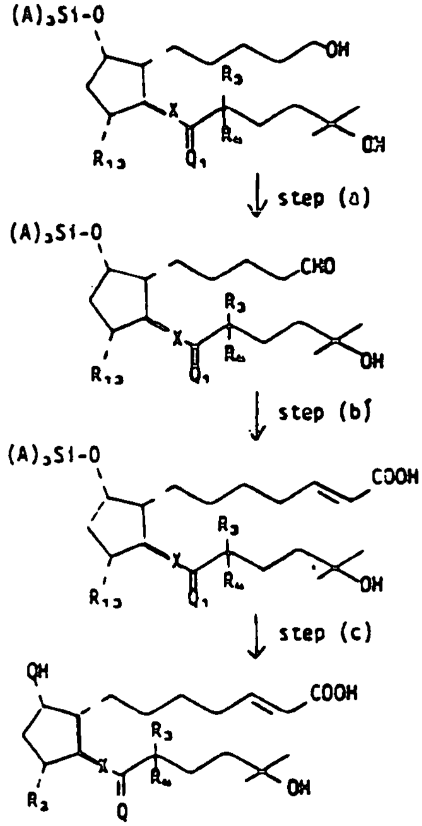
CXCIX

CCXVI

CCXVII

CCXVIII

CHART 38



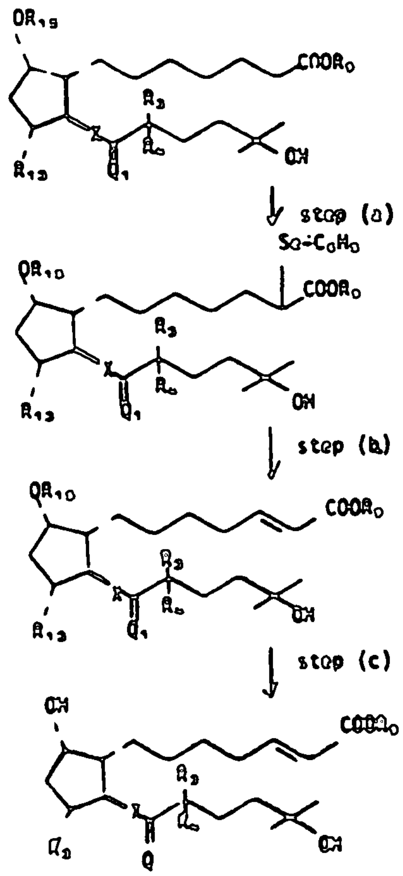
CCXIX

CCXX

CCXXI

CCXXII

CHART 39



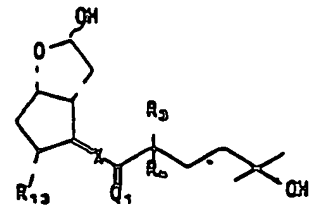
CCXXIII

CCXXIV

CCXXV

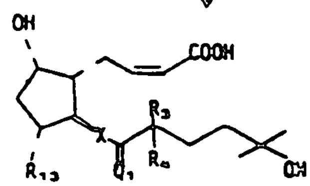
CCXXVI

CHART 40



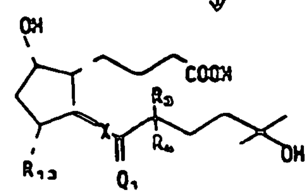
CXCIX

↓ step (a)



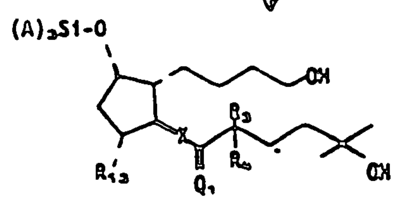
CCXXVII

↓ step (b)



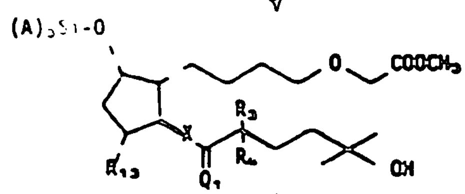
CCXXVIII

↓ step (c)



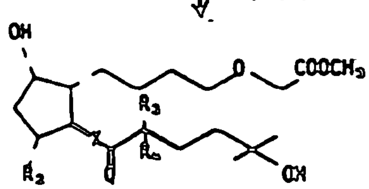
CCXXIX

↓ step (d)



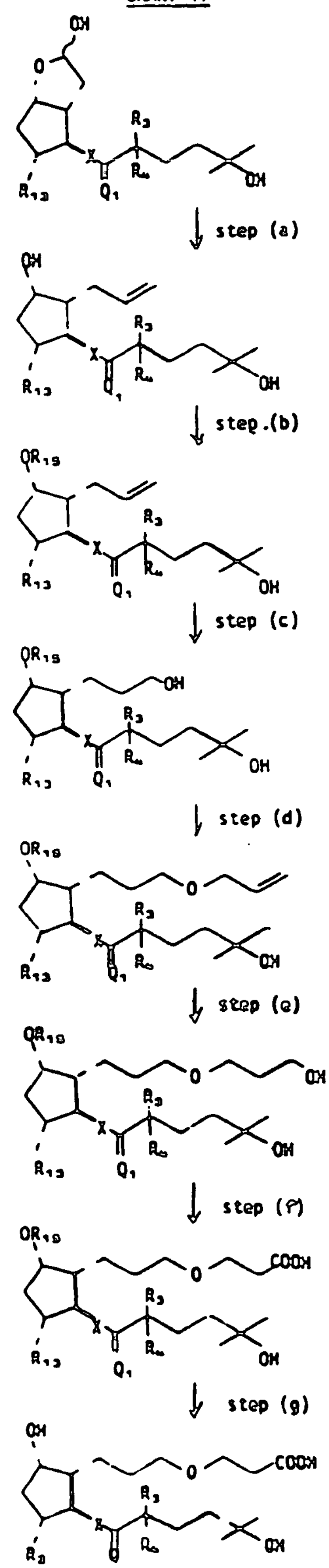
CCXXX

↓ step (e)



CCXXXI

CHART 41



CXCIX

CCXXXII

CCXXXIII

CCXXXIV

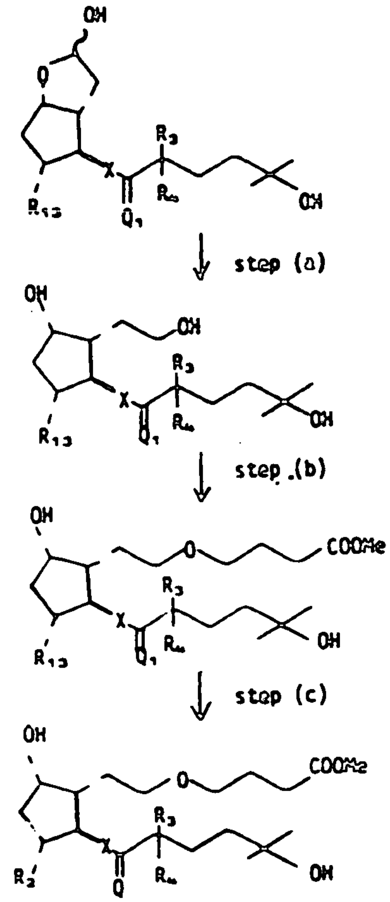
CCXXXV

CCXXXVI

CCXXXVII

CCXXXVIII

CHART 42



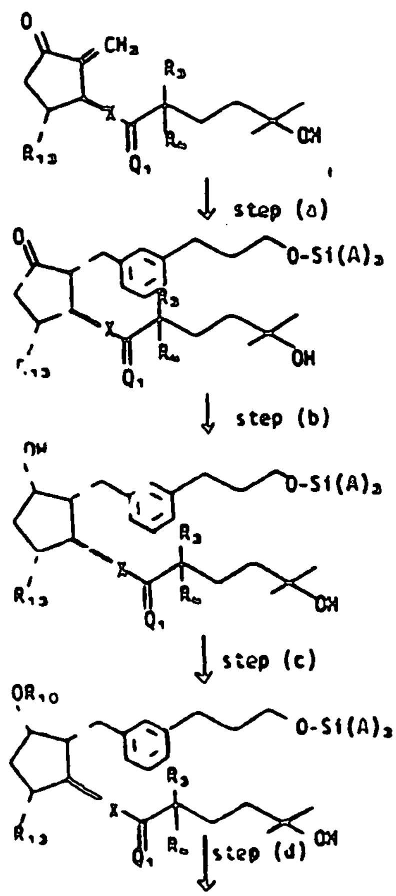
CXCIX

CCXXXIX

CCXL

CCXLI

CHART 43



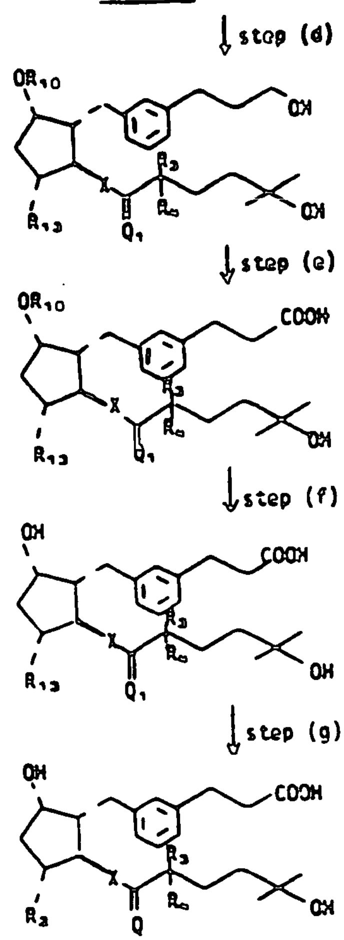
CCXLIII

CCXLIV

CCXLV

CCXLVI

CHART 43 (continued)



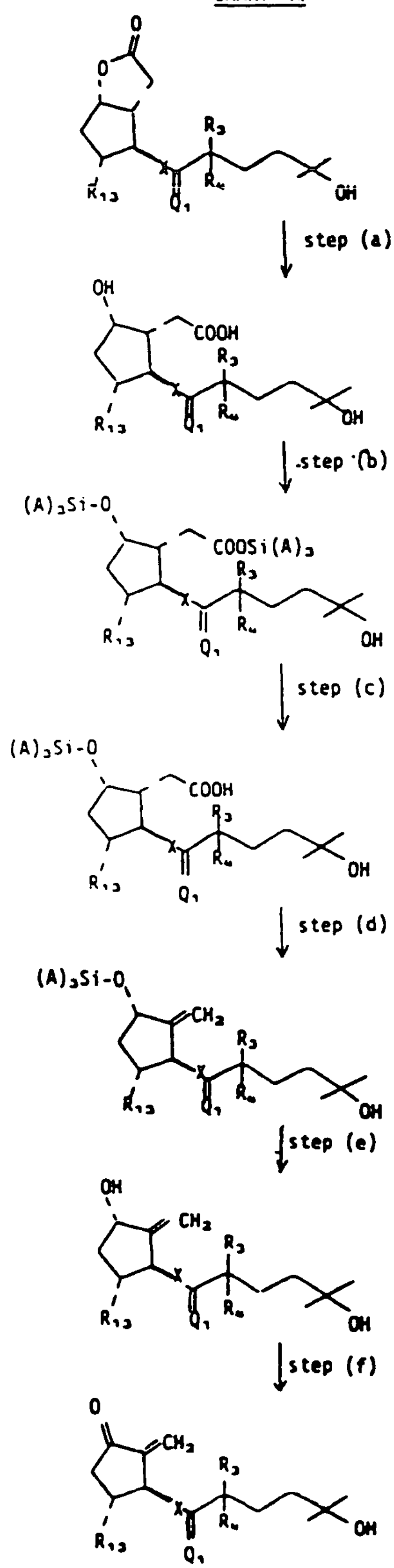
CCXLVII

CCXLVIII

CCXLIX

CCL

CHART 44



CXCVIII

CCLI

CCLII

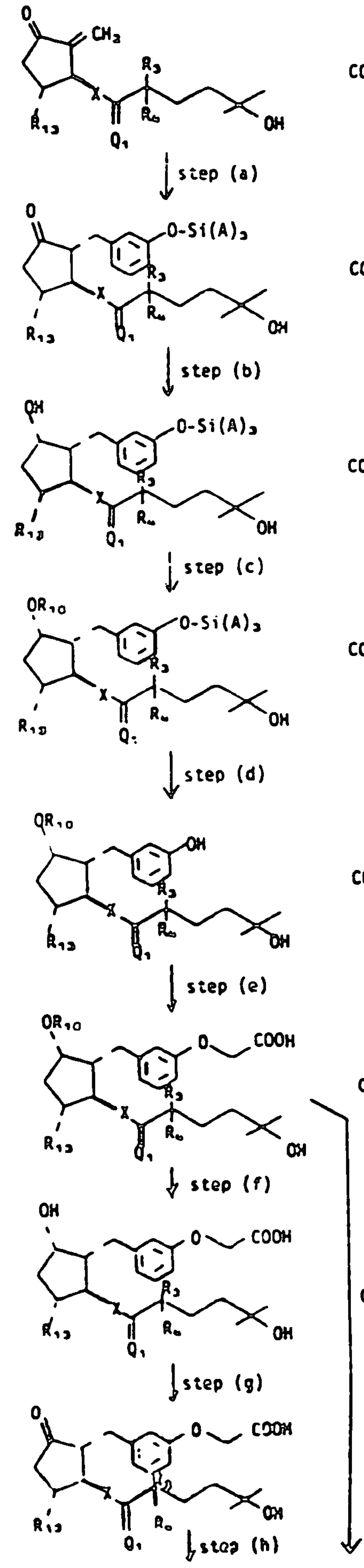
CCLIII

CCLIV

CCLV

CCXLIII

CHART 45



CCXLIII

CCLVI

CCLVII

CCLVIII

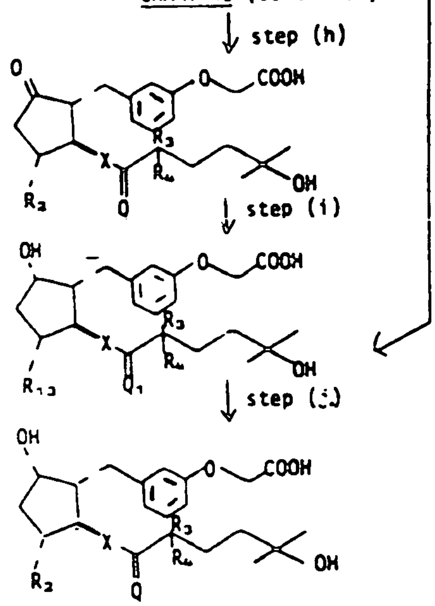
CCLIX

CCLX

CCLXI

CCLXII

CHART 45 (continued)

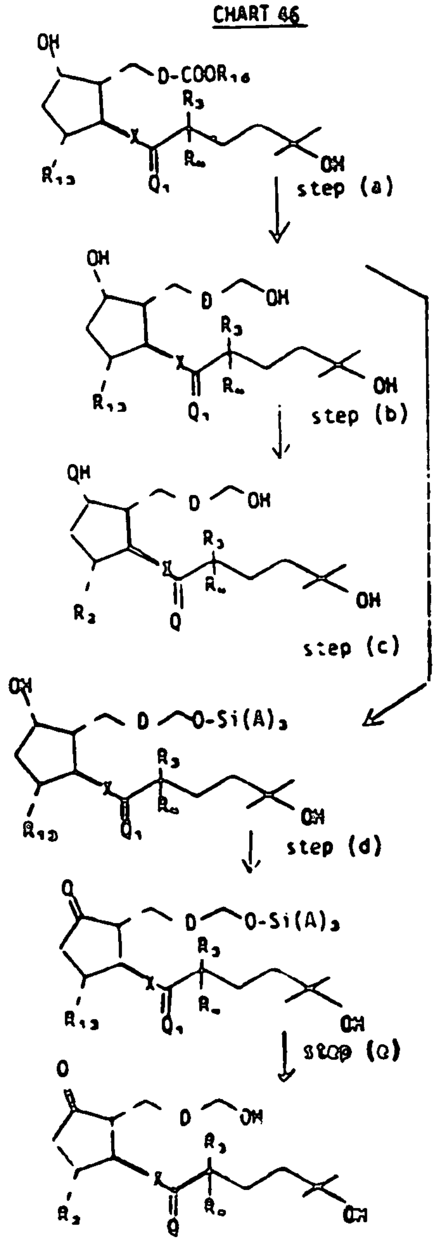


CCLXIII

CCLXIV

CCLXV

CHART 46



CCLXVI

CCLXVII

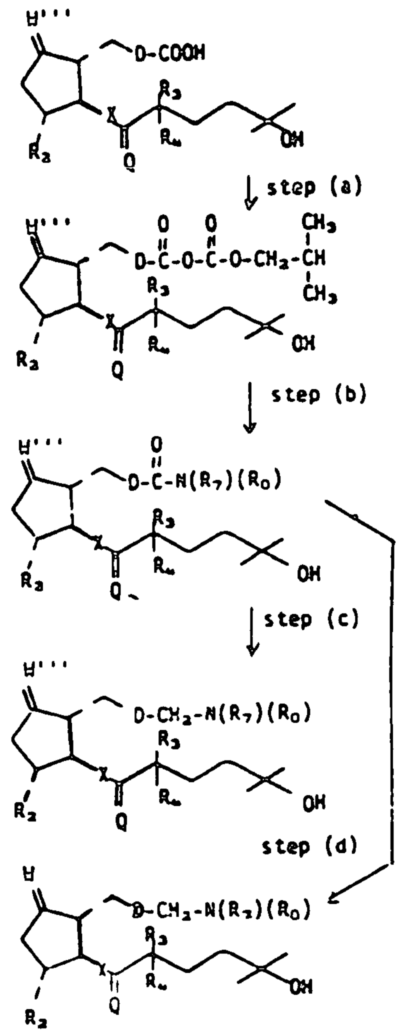
CCLXVIII

CCLXIX

CCLXX

CCLXXI

CHART 47



CCLXXII

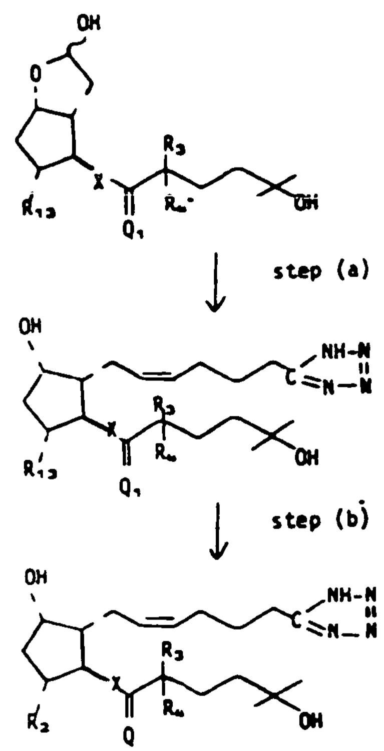
CCLXXIII

CCLXXIV

CCLXXV

CCLXXVI

CHART 48

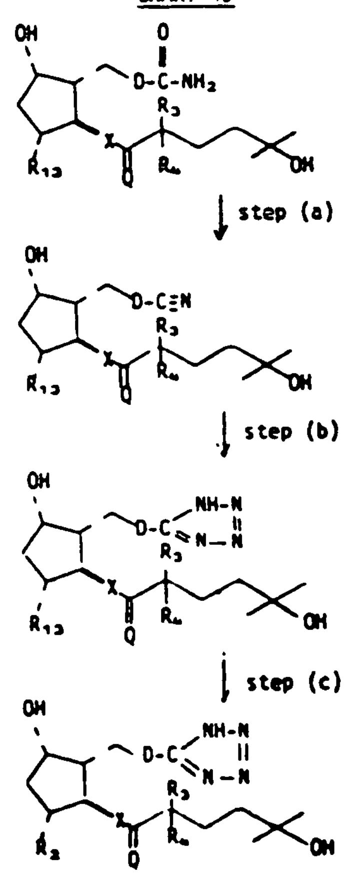


CXCIX

CCLXXVII

CCLXXVIII

CHART 49



CCLXXIX

CCLXXX

CCLXXXI

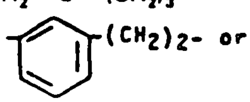
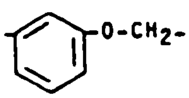
CCLXXXII

TABLE
DEFINITION OF TERMS FOR FORMULAS

A is

alkyl of one to 4 carbon atoms, inclusive, phenyl, phenyl substituted with one to 2 fluoro, chloro, or alkyl of one to 4 carbon atoms, inclusive, or aralkyl of 7 to 12 carbon atoms, inclusive, the A groups being the same or different.

D is

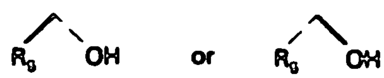
(1) cis-$CH=CH—CH_2—(CH_2)_g—CH_2—$
(2) cis-$CH=CH—CH_2—(CH_2)_g—CF_2—$
(3) cis-$CH_2—CH=CH—CH_2—CH_2—$
(4) trans-$(CH_2)_3—CH=CH—$
(5) $—(CH_2)_3—(CH_2)_g—CH_2—$
(6) $—(CH_2)_3—CH_2—CF_2—$
(7) $—(CH_2)_3—O—CH_2—$
(8) $—(CH_2)_2—O—(CH_2)_2—$
(9) $—CH_2—O—(CH_2)_3—$
(10) 
(11) 

wherein g is zero, one, two, or three.

Hal is

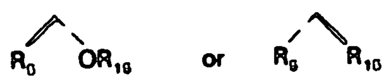
chloro, bromo, or iodo.

Q is



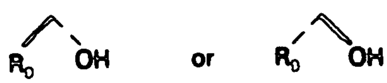
wherein R_8 is hydrogen or alkyl of one to 4 carbon atoms, inclusive.

Q_1 is



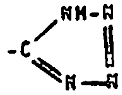
wherein R_8 is hydrogen or alkyl of one to 4 carbon atoms, inclusive and R_{10} is a blocking group as defined below.

Q_2 is

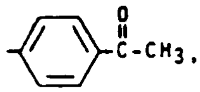


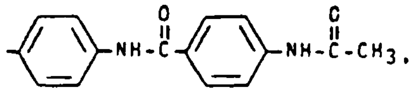
wherein R_0 is alkyl of one to 4 carbon atoms, inclusive.

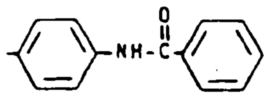
R_1 is

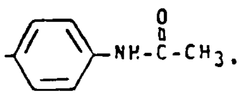
(1) $—COOR_0$
(2) $—CH_2OH$
(3) $—CH_2N(R_7)(R_0)$
(4) $—C(=O)—N(R_7)(R_0)$
(5) $—C(=O)—NH—SO_2—R_{30}$ or
(6) 

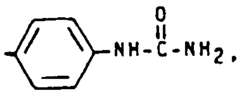
wherein R_0 is (a) hydrogen, (b) alkyl of one to 12 carbon atoms, inclusive, (c) cycloalkyl of 3 to 10 carbon atoms, inclusive, (d) aralkyl of 7 to 12 carbon atoms, inclusive, (e) phenyl, (f) phenyl substituted with one, 2, or 3 chloro or alkyl groups of one to 3 carbon atoms, inclusive;

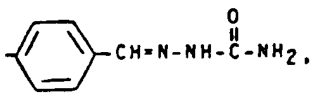
(g) 

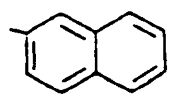
(h) 

(i) 

(j) 

(k) 

(l) 

(m) 

(n) $-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-R_{20}$,

wherein R_{20} is phenyl, p-bromophenyl, p-biphenylyl, p-nitrophenyl, p-benzamidophenyl, or 2-naphthyl, or

(o) a pharmacologically acceptable cation; wherein R_7 and R_0 are hydrogen, alkyl of one to 12 carbon atoms, inclusive, benzyl, or phenyl, being the same or different, and wherein R_{20} is hydrogen, alkyl of one to 12 carbon atoms, inclusive, phenyl, phenyl substituted with one, 2, or 3 chloro or alkyl groups of one to 3 carbon atoms, inclusive, or phenyl substituted with hydroxycarbonyl or alkoxycarbonyl of one to 4 carbon atoms, inclusive,

R_2 is

hydrogen, hydroxyl, or hydroxymethyl.

R_3 and R_4 are

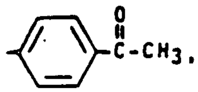
hydrogen, alkyl of one to 4 carbon atoms, inclusive, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

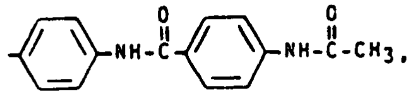
R_5 is

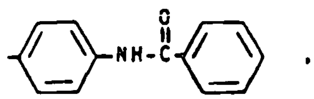
hydrogen or alkyl of one to 4 carbon atoms, inclusive.

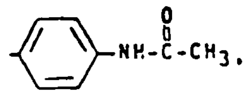
R_0 is

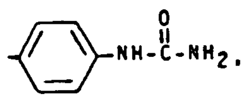
(a) hydrogen, (b) alkyl of one to 12 carbon atoms, inclusive, (c) cycloalkyl of 3 to 10 carbon atoms, inclusive, (d) aralkyl of 7 to 12 carbon atoms, inclusive, (e) phenyl, (f) phenyl substituted with one, 2, or 3 chloro or alkyl groups of one to 3 carbon atoms, inclusive;

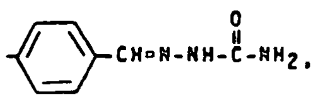
(g) 

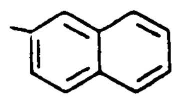
(h) 

(i) 

(j) 

(k) 

(l) 

(m) 

(n) $-CH_2-\overset{\overset{O}{\|}}{C}-R_{20}$,

wherein R_{20} is phenyl, p-bromophenyl, p-biphenylyl, p-nitrophenyl, p-benzamidophenyl, or 2-naphthyl, or

(o) a pharmacologically acceptable cation.

R_7 and R_8 are
hydrogen, alkyl of one to 12 carbon atoms, inclusive, benzyl, or phenyl, being the same or different.

R_9 is
alkyl of one to 4 carbon atoms, inclusive.

R_{10} and R_{11} are
hydrogen or fluoro.

R_{12} is
alkyl of one to 12 carbon aotms, inclusive.

R_{13} is
hydrogen, $-OR_{18}$, or $-CH_2OR_{18}$, wherein R_{18} is a blocking group defined below.

R_{14} is
hydrogen, $-OR_{19}$, or $-CH_2OR_{19}$, wherein R_{19} is a carboxyacyl blocking group defined below.

R_{18} is
a blocking group including tetrahydropyranyl, tetrahydrofuranyl, or a group of the formula

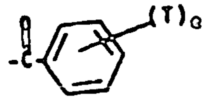
$$R_{21}-O-\underset{R_{22}}{\overset{|}{C}}-\underset{R_{23}}{\overset{H}{C}}-R_{24}$$

wherein R_{21} is alkyl of one to 18 carbon atoms, inclusive, cycloalkyl of 3 to 10 carbon atoms, inclusive, aralkyl of 7 to 12 carbon atoms, inclusive, phenyl, or phenyl substituted with one, 2 or 3 alkyl of one to 4 carbon atoms, inclusive, wherein R_{22} and R_{23} are the same or different, being hydrogen, alkyl of one to 4 carbon atoms, inclusive, phenyl or phenyl substituted with one, 2 or 3 alkyl of one to 4 carbon atoms, inclusive, or when R_{22} and R_{23} are taken together, $-(CH_2)_a-$ or $-(CH_2)_b-O-(CH_2)_c-$ wherein a is 3, 4, or 5, b is one, 2, or 3, and c is one, 2, or 3 with the proviso that b plus c is 2, 3, or 4, and wherein R_{24} is hydrogen or phenyl.

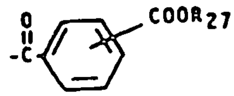
R_{19} is
hydrogen or methyl.

R_{17} is
hydrocarbyl of one to 18 carbon atoms, inclusive.

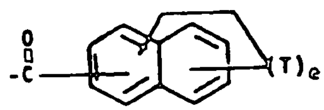
R_{18} is
carboxyacyl including

(a) 

wherein "T" is alkyl of one to 4 carbon atoms, inclusive, bromo, phenylalkyl of 7 to 10 carbon atoms, inclusive, or nitro, and "e" is zero to 5, inclusive, provided that not more than two T's are other than alkyl, and that the total number of carbon atoms in the T's does not exceed 10 carbon atoms.

(b) 

wherein R_{27} is alkyl of one to 4 carbon atoms, inclusive,

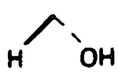
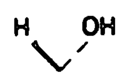
(c) 

wherein "T" and "e" are as defined above, or

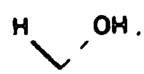
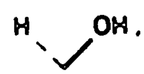
(d) $-\overset{\overset{\displaystyle O}{\|}}{C}-R_{25}$

wherein R_{25} is hydrogen, alkyl of one to 19 carbon atoms, inclusive, or alkyl of 7 to 12 carbon atoms, inclusive, wherein alkyl or aralkyl are substituted with zero to 3 halo atoms.

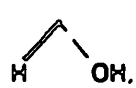
R_{19} is
the same as R_1 but with the proviso that R_{19} is not —COOH or —$COOR_{12}$ wherein R_{12} is alkyl of one to 12 carbon atoms, inclusive, when (A) R_2 is hydroxy, R_3 and R_4 are hydrogen, Q is

 W is  or 

and either (1) D is cis-CH=CH—CH_2—$(CH_2)_g$—CH_2— and X is trans-CH=CH—, or (2) D is —$(CH_2)_3$—$(CH_2)_g$—CH_2— and X is trans-CH=CH— or —CH_2CH_2—, (B) R_2, R_3, and R_4 are hydrogen, W is

  or 

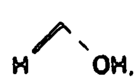
D is —$(CH_2)_3$—$(CH_2)_g$—CH_2—, and X is trans-CH=CH—, or (C) R_2, R_3, and R_4 are hydrogen, Q is



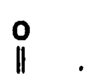
W is 

D is cis-CH=CH—CH_2—$(CH_2)_g$—CH_2— and X is trans-CH=CH—.

R_{20} is
the same as R_1 but with the proviso that R_{20} is not —COOH or —$COOR_{12}$ wherein R_{12} is alkyl of one to 12 carbon atoms, inclusive, when Q is



R_2 is hydroxy, R_3 and R_4 are hydrogen, W is



and either (1) D is cis-CH=CH—CH_2—$(CH_2)g$—CH_2— and X is trans-CH=CH—, or (2) D is —$(CH_2)_3$—$(CH_2)_g$—CH_2— and X is —CH_2CH_2—.

R_{21} is
alkyl of one to 18 carbon atoms, inclusive, cycloalkyl of 3 to 10 carbon atoms, inclusive, aralkyl of 7 to 12 carbon atoms, inclusive, phenyl, or phenyl substituted with one, 2, or 3 alkyl of one to 4 carbon atoms, inclusive.

R_{22} and R_{23} are
hydrogen, alkyl of one to 4 carbon atoms, inclusive, phenyl or phenyl substituted with one, 2, or 3 alkyl of one to 4 carbon atoms, inclusive, being the same or different, or, when R_{22} and R_{23} are taken together, —$(CH_2)_a$— or —$(CH_2)_b$—O—$(CH_2)_c$— wherein, a is 3, 4, or 5, b is one, 2, or 3, and c is one, 2, or 3 with the proviso that b plus c is 2, 3, or 4.

R_{24} is
hydrogen or phenyl.

R_{25} is
hydrogen, alkyl of one to 19 carbon atoms, inclusive, or aralkyl of 7 to 12 carbon atoms, inclusive, wherein alkyl or aralkyl are substituted with zero to 3 halo atoms.

R_{26} is
alkyl of one to 3 carbon atoms, inclusive.

R_{27} is
alkyl of one to 4 carbon atoms, inclusive.

R_{28} is
phenyl, p-bromophenyl, p-biphenylyl, p-nitrophenyl, p-benzamidophenyl, or 2-naphthyl.

R_{29} is
hydrogen, alkyl of one to 12 carbon atoms, inclusive, aralkyl of 7 to 12 carbon atoms, inclusive, phenyl, phenyl substituted with one, 2, or 3 chloro or alkyl groups of one to 3 carbon atoms, inclusive, or phenyl substituted with hydroxycarbonyl or alkoxycarbonyl in which the alkoxy group consists of one to 4 carbon atoms, inclusive.

R_{30} is
alkyl of one to 10 carbon atoms, inclusive, aralkyl of 7 to 12 carbon atoms, inclusive, phenyl, or phenyl substituted with one or 2 chloro or alkyl groups of one to 3 carbon atoms, inclusive.

R_{31} is
R_1, R_{10}, or R_{20}.

R_{32} is
—$CH{=}CH_2$ or —$C(CH_3)(OH)$—CH_3 when R_{31} is R_1,
—$CH(OH)$—CH_3 when R_{31} is R_{10}, or —CO—CH_3 when R_{31} is —R_{20}.

$(T)_e$ is
alkyl of one to 4 carbon atoms, inclusive, phenylalkyl of 7 to 10 carbon atoms, inclusive, or nitro, and e is zero to 5, inclusive, provided that not more than two T's are other than alkyl, and that the total number of carbon atoms in the T's does not exceed 10 carbon atoms.

THP is
tetrahydropyran-2-yl.

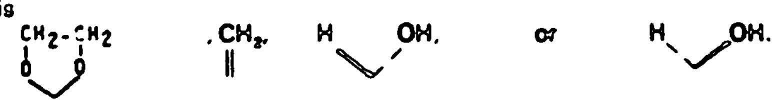
W is

W' is

W" is

wherein A is as defined above.

W''' is



X is
cis- or trans-CH=CH—, —C≡C—, or —CH_2CH_2—.

a is
3, 4, or 5.

b is
one, 2, or 3.

c is
one, 2, or 3 with the proviso that b plus c is 2, 3, or 4.

e is
zero, one, 2, 3, 4, or 5.

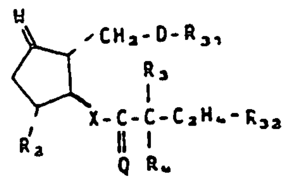
g is
zero, one, 2, or 3.

j is
one, 2, or 3.

p is
one, 2, or 3 with th proviso that j plus p is 4.

CLAIMS

1. A compound of the formula



wherein D is

(1) *cis*-$CH=CH—CH_2—(CH_2)_g—CH_2—$,
(2) *cis*-$CH=CH—CH_2—(CH_2)_g—CF_2—$,
(3) *cis*—$CH_2—CH=CH—CH_2—CH_2—$,
(4) *trans*-$(CH_2)_3—CH=CH—$,
(5) $—(CH_2)_3—(CH_2)_g—CH_2—$,
(6) $—(CH_2)_3—CH_2—CF_2—$,
(7) $—(CH_2)_3—O—CH_2—$,
(8) $—(CH_2)_2—O—(CH_2)_2—$,
(9) $—CH_2—O—(CH_2)_3—$,
(10) $—W_3—(CH_2)_2—$ or
(11) $—W_3—O—CH_2$

in which W_3 is 1,3-phenylene and g is one, 2 or 3; Q is α-OH:β-H, α-OH:β-CH_3, α-H:β-OH or α-CH_3:β-OH;
R_2 is hydrogen, hydroxyl or hydroxymethyl; R_3 and R_4 are independently selected from hydrogen, C_{1-4} alkyl and fluorine, provided that $—CR_3R_4—$ is not —CFAlkyl-;
W is oxo, methylene, α-OH:β-H or α-H:β-OH;

R_{31} is (1) $—COOR_6$
(2) $—CH_2OH$
(3) $—CH_2—NR_7R_8$
(4) $—CO—NR_7R_8$
(5) $—CO—NH—COO—R_{20}$ or
(6) 5-tetrazolyl

in which R_6 is hydrogen, C_{1-12} alkyl, C_{3-10} cycloalkyl, C_{7-12} aralkyl, phenyl, phenyl substituted one to 3 times by chlorine atoms or C_{1-3} alkyl radicals, $—W_4—CO—CH_3$, $—W_4—NH—CO—W_4—NH—CO—CH_3$, $—W_4—NH—CO—Ph$, $—W_4—NH—CO—CH_3$, $—W_4—NH—CO—NH_2$, $—W_4—CH=N—NH—CO—NH_2$, 2-naphthyl, $—CH_2—CO—Ph$, $—CH_2—CO—W_4—Br$, $—CH_2—CO—W_4—Ph$, $—CH_2—CO—W_4—NO_2$, $—CH_2—CO—W_4—NH—CO—Ph$, (2-naphthyl)carbonylmethyl or a pharmacologically acceptable cation, W_4 being 1,4-phenylene and Ph being phenyl; R_7 and R_8 are independently selected from hydrogen, C_{1-12} alkyl, benzyl and phenyl; and R_{20} is hydrogen, C_{1-12} alkyl, phenyl, phenyl substituted one to 3 times by chlorine atoms or C_{1-3} alkyl radicals, hydroxycarbonylphenyl or (C_{1-4} alkoxy)carbonylphenyl;
X is *cis*-CH=CH—, *trans*-CH=CH, —C≡C— or $—CH_2CH_2—$; and
R_{32} is - $—CH=CH_2$, $—C(CH_3)_2(OH)$, $—CH(OH)—CH_3$ or $—CO—CH_3$, with the provisos that R_{32} is only $—CH(OH)—CH_3$ when R_{31} is R_{10} as defined herein and that R_{32} is only $—CO—CH_3$ when R_{31} is R_{23} as defined herein.

2. A compound according to claim 1, selected from the group consisting of:
19,20-Didehydro-PGF$_2\alpha$, methyl ester,
15(R)-19,20-Didehydro-PGF$_2\alpha$, methyl ether,
2-Decarboxy-2-hydr xymethyl-19,20-didehydro-PGF$_2\alpha$,
2-Decarboxy-2-hydr xymethyl-11-deoxy-19,20-didehydr -PGF$_2\alpha$,
2-Decarboxy-2-hydr xymethyl-11-deoxy-11α-hydroxymethyl-19,20-didehydro-PGF$_2\alpha$,
2-Decarboxy-2-hydroxymethyl-19,20-didehydro-PGF$_2\beta$,
2-Decarboxy-2-hydr xymethyl-11-deoxy-19,20-didehydro-PGF$_2\beta$,
2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-19,20-didehydro-PGF$_2\beta$,
2-Decarboxy-2-hydroxymethyl-19,20-didehydro-PGE$_2$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-19,20-didehydro-PGE$_2$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-19,20-didehydro-PGE$_2$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-19,20-didehydro-PGE$_2$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-19,20-didehydro-PGE$_2$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-19,20-didehydro-PGE$_2$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-15(S)-15-methyl-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-16,16-difluoro-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-11-deoxy-PGFO$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-11-deoxy-15(S)-15-methyl-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-11-deoxy-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-11-deoxy-16,16-difluoro-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-11-deoxy-11α-hydroxymethyl-16,16-difluoro-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-15(S)-15-methyl-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-16,16-difluoro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-11-deoxy-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-11-deoxy-15(S)-15-methyl-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-11-deoxy-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-11-deoxy-16,16-difluoro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-11-deoxy-11α-hydroxymethyl-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-11-deoxy-11α-hydroxymethyl-16,16-difluoro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-15(S)-15-methyl-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-16,16-difluoro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-11-deoxy-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-11-deoxy-15(S)-15-methyl-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-11-deoxy-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-11-deoxy-16,16-difluoro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-11-deoxy-11α-hydroxymethyl-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-11-deoxy-11α-hydroxymethyl-16,16-difluoro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-9-deoxo-9-methylene-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-9-deoxo-9-methylene-15(S)-15-methyl-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-9-deoxo-9-methylene-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-9-deoxo-9-methylene-16,16-difluoro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-9-deoxo-9-methylene-11-deoxy-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-9-deoxo-9-methylene-15(S)-15-methyl-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-9-deoxo-9-methylene-11-deoxy-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-9-deoxo-9-methylene-11-deoxy-16,16-difluoro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-4,5,19,20-tetradehydro-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-PGE₁.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-PGE₁.

2-Decarboxy-2-hydroxymethyl-4,5,13,14,19,20-hexadehydro-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-16,16-difluoro-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-PGF₁α.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-16,16-difluoro-PGF₁α.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-15(S)-15-methyl-PGF₁α.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-PGF₁α.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-16,16-difluoro-PGF₁α.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-15(S)-15-methyl-PGF₁α.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-PGF₁α.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-16,16-difluoro-PGF₁α.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-PGF₁α.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-PGF₁β.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-16,16-difluoro-PGF₁β.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-15(S)-methyl-PGF₁β.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-PGf₁β.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-16,16-difluoro-PGF₁β.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-15(S)-15-methyl-PGF₁β.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-PGF₁β.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-16,16-difluoro-PGF₁β.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-PGF₁β.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-16,16-difluoro-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-15(S)-15-methyl-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-16,16-difluoro-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-15(S)-15-methyl-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-16,16-difluoro-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-9-deoxo-9-methylene-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-9-deoxo-9-methylene-16,16-difluoro-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-9-deoxo-9-methylene-15(S)-15-methyl-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-9-deoxo-9-methylene-11-deoxy-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-9-deoxo-9-methylene-11-deoxy-16,16-difluoro-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-9-deoxo-9-methylene-11-deoxy-15(S)-15-methyl-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-16,16-difluoro-PGE₁.

2-Decarboxy-2-hydroxymethyl-2,3,19,20-tetradehydro-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-PGE₁.

2-Decarboxy-2-hydroxymethyl-19,20-didehydro-PGF₁α.

2-Decarboxy-2-hydroxymethyl-16,16-dimethyl-19,20-didehydro-PGF₁α.

2-Decarboxy-2-hydroxymethyl-16,16-difluoro-19,20-didehydro-PGF₁α.

2-Decarboxy-2-hydroxymethyl-13,14-dihydro-19,20-didehydro-PGF₁α.

2-Decarboxy-2-hydroxymethyl-11-deoxy-19,20-didehydro-PGF₁α.

2-Decarboxy-2-hydroxymethyl-11-deoxy-16,16-dimethyl-19,20-didehydro-PGF₁α.

2-Decarboxy-2-hydroxymethyl-11-deoxy-16,16-difluoro-19,20-didehydro-PGF₁α.

2-Decarboxy-2-hydroxymethyl-11-deoxy-13,14-dihydro-19,20-didehydro-PGF₁α.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-19,20-didehydro-PGF₁α.

2-D carboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-16,16-dimethyl-19,20-didehydro-PGF$_1\alpha$.

2-D carboxy-2-hydr xymethyl-11-deoxy-11α-hydroxym thyl-16,16-difluoro-19,20-didehydro-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-13,14-dihydro-19,20-didehydro-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-19,20-didehydro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-16,16-dimethyl-19,20-didehydro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-16,16-difluoro-19,20-didehydro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-13,14-dihydro-19,20-didehydro-PGF$_2\beta$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-19,20-didehydro-PGF$_1\alpha$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-16,16-dimethyl-19,20-didehydro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-16,16-difluoro-19,20-didehydro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-13,14-dihydro-19,20-didehydro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-19,20-didehydro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-16,16-dimethyl-19,20-didehydro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-16,16-difluoro-19,20-didehydro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-13,14-dihydro-19,20-didehydro-PGF$_1\beta$.

2-Decarboxy-2-hydroxymethyl-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-16,16-dimethyl-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-16,16-difluoro-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-13,14-dihydro-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-16,16-dimethyl-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-16,16-difluoro-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-13,14-dihydro-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-16,16-dimethyl-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-16,16-difluoro-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-13,14-dihydro-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-9-deoxy-9-methylene-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-16,16-dimethyl-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-16,16-difluoro-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-13,14-dihydro-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-16,16-dimethyl-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-16,16-difluoro-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-13,14-dihydro-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-16,16-dimethyl-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-1,314-dihydro-19,20-didehydro-PGE$_1$.

2-Decarboxy-2-hydroxymethyl-19(R)-19-hydroxy-PGF$_2\alpha$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-19(R)-19-hydroxy-PGF$_2\alpha$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-19(R)-19-hydroxy-PGF$_2\alpha$.

2-Decarboxy-2-hydroxymethyl-19(R)-19-hydroxy-PGF$_2\beta$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-19(R)-19-hydroxy-PGF$_2\beta$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-19(R)-19-hydroxy-PGF$_2\beta$.

2-Decarboxy-2-hydroxymethyl-19(R)-19-hydroxy-PGE$_2$.

2-Decarboxy-2-hydroxymethyl-11-deoxy-19(R)-19-hydroxy-PGE$_2$.

2-Decarboxy-2-hydroxymethyl-11α-hydroxymethyl-19(R)-19-hydroxy-PGE$_2$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-19(R)-19-hydroxy-PGE$_2$.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-19(R)-19-hydroxy-PGE_2.

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-19(R)-19-hydroxy-PGE_2.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-15(S)-15-methyl-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-16,16-difluoro-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-11-deoxy-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-11-deoxy-15(S)-15-methyl-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-11-deoxy-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-11-deoxy-16,16-difluoro-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5-dideoxy-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5-dideoxy-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5-dideoxy-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-$PGE_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-16,16-difluoro-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-4,5,-didehydro-19(R)-19-hydroxy-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-15(S)-15-methyl-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-16,6-difluoro-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-11-deoxy-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-11-deoxy-15(S)-15-methyl-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-11-deoxy-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-11-deoxy-16,16-difluoro-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-16,16-difluoro-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-15(S)-15-methyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-16,16-difluoro-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-11-deoxy-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-11-deoxy-15(S)-15-methyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-11-deoxy-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-11-deoxy-16,16-difluoro PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-16,16-difluoro-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-15(S)-15-methyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-PGE_1.

2-D carboxy-2-hydroxymethyl-4,5,13,14-tetradehydr -19(R)-19-hydr xy-9-deoxo-9-methylene-16,16-difluoro-PGE_1.

2-Decarboxy-2-hydr xym thyl-4,5-didehydro-19(R)-19-hydroxy-9-de xo-9-methylene-11-deoxy-PGE_1.

2-Decarboxy-2-hydroxym thyl-4,5-didehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-15(S)-15-methyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-11-deoxy-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-11-deoxy-16,16-difluoro-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5-didehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-4,5,13,14-tetradehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-16,16-difluoro-PGE_1.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-1i(R)-19-hydroxy-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-16,16-difluoro-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydeo-19(R)-19-hydroxy-15(S)-15-methyl-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-16,16-difluoro-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-15(S)-15-methyl-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-16,16-difluoro-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-$PGF_1\alpha$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-16,16-difluoro-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-15(S)-methyl-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-16,16-difluoro-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-15(S)-15-methyl-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-16,16-dimethyl-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-$PGF_1\beta$.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-PGE_1.

2 Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-16,16-difluoro-PGE_1.

2 Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-15(S)-15-methyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-PGE_1.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-16,16-difluoro-PGE_1.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-15(S)-15-methyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy11-deoxy-11α-hydroxymethyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-11-deoxy-11α-hydroxymethyl-16,16-difluoro-PGE_1.

2-Decarboxy-2-hydr xymethyl-2,3-didehydro-19(R)-19-hydr xy-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-PGE_1.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydr xy-9-deoxo-9-methylene-PGE_1.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydr xy-9-deoxo-9-methylene-16,16-difluoro-PGE_1.

2-Decarboxy-2-hydr xymethyl-2,3-didehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-15(S)-15-m thyl-PGE_1.

2-Decarboxy-2-hydr xymethyl-2,3-didehydro-19(R)-19-hydroxy-9-deox -9-methylene-11-deoxy-PGE_1.

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-11-deoxy-16,16-difluoro-PGE_1,

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-11-deoxy-15(S)-15-methyl-PGE_1,

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-PGE_1,

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-16,16-difluoro-PGE_1,

2-Decarboxy-2-hydroxymethyl-2,3-didehydro-19(R)-19-hydroxy-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-15(S)-15-methyl-PGE_1,

2-Decarboxy-2-hydroxymethyl-19(R)-19-hydroxy-$PGE_1\alpha$,

2-Decarboxy-2-hydroxymethyl-16,16-dimethyl-19(R)-19-hydroxy-$PGF_1\alpha$,

2-Decarboxy-2-hydroxymethyl-16,16-difluoro-19(R)-19-hydroxy-$PGF_1\alpha$,

2-Decarboxy-2-hydroxymethyl-13,14-dihydro-19(R)-19-hydroxy-$PGF_1\alpha$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-19(R)-19-hydroxy-$PGF_1\alpha$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-16,16-dimethyl-19(R)-19-hydroxy-$PGF_1\alpha$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-16,16-difluoro-19(R)-19-hydroxy-$PGF_1\alpha$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-13,14-dihydro-19(R)-19-hydroxy-$PGF_1\alpha$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-19(R)-19-hydroxy-$PGF_1\alpha$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-16,16-dimethyl-19(R)-19-hydroxy-$PGF_1\alpha$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-16,16-difluoro-19(R)-19-hydroxy-$PGF_1\alpha$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-13,14-dihydro-19(R)-19-hydroxy-$PGF_1\alpha$,

2-Decarboxy-2-hydroxymethyl-19(R)-19-hydroxy-$PGF_1\beta$,

2-Decarboxy-2-hydroxymethyl-16,16-dimethyl-19(R)-19-hydroxy-$PGF_1\beta$,

2-Decarboxy-2-hydroxymethyl-16,16-difluoro-19(R)-19-hydroxy-$PGF_1\beta$,

2-Decarboxy-2-hydroxymethyl-13,14-dihydro-19(R)-19-hydroxy-$PGF_1\beta$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-19(R)-19-hydroxy-$PGF_1\beta$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-16,16-dimethyl-19(R)-19-hydroxy-$PGF_1\beta$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-16,16-difluoro-19(R)-19-hydroxy-$PGF_1\beta$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-13,14-dihydro-19(R)-19-hydroxy-$PGF_1\beta$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-19(R)-19-hydroxy-$PGF_1\beta$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-16,16-dimethyl-19(R)-19-hydroxy-$PGF_1\beta$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-16,16-difluoro-19(R)-19-hydroxy-$PGF_1\beta$,

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-13,14-dihydro-19(R)-19-hydroxy-$PGF_1\beta$,

2-Decarboxy-2-hydroxymethyl-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-16,16-dimethyl-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-16,16-difluoro-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-13,14-dihydro-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-11-deoxy-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-11-deoxy-16,16-dimethyl-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-11-deoxy-16,16-difluoro-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-11-deoxy-13,14-dihydro-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-19(R)-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-16,16-dimethyl-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-16,16-difluoro-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-11-deoxy-11α-hydroxymethyl-13,14-dihydro-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-16,16-dimethyl-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-16,16-difluoro-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-13,14-dihydro-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-16,16-dimethyl-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-16,16-difluoro-19(R)-19-hydroxy-PGE_1,

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-13,14-dihydro-19(R)-19-hydroxy-PGE$_1$,

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-19(R)-19-hydroxy-PGE$_1$,

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-16,16-dimethyl-19(R)-19-hydroxy-PGE$_1$,

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-16,16-difluoro-19(R)-19-hydroxy-PGE$_1$, and

2-Decarboxy-2-hydroxymethyl-9-deoxo-9-methylene-11-deoxy-11α-hydroxymethyl-13,14-dihydro-19(R)-19-hydroxy-PGE$_1$.

3. A compound as claimed in claim 1 substantially as herein described.

4. A pharmaceutical composition comprising a compound as claimed in any preceding claim in association with a physiologically acceptable excipient.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1980. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.